CORONARY HEART DISEASE

Angina Pectoris; Myocardial Infarction



William Heberden 1710—1801 Courtesy of Royal College of Physicians

Coronary Heart Disease

ANGINA PECTORIS; MYOCARDIAL INFARCTION

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FOREWORD by WILLIAM DOCK, M.D.



A HOEBER-HARPER BOOK

CORONARY HEART DISEASE, Angina Pectoris; Myocardial Infarction

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TO HELEN
and to our children,
Elizabeth, Paul, Sarah, and John

FOREWORD

CORONARY ARTERIAL disease is the most human of all illnesses. It never occurs in other vertebrates unless they are subjected to the most drastic changes in diet, and is unknown among primitive races of man It first appears with the pastoral stage of civilization, and then only among the most prosperous families Today it is practically unknown among hundreds of millions of people who live on the verge of starvation It enters medical history with a prosperous knight, one of William Harvey's patients, becomes an established diagnosis—angina pectoris—with Heberden's robust squires, and enters the twentieth century with Osler's "business men, eating, drinking and smoking to excess." In the book prepared by my colleague, Dr. Milton Plotz, this fascinating disease, of urgent concern to its many physician victims, has been given a lively and thoroughly modern description

The history of coronary artery disease may be divided into three phases One begins with Harvey's second letter to Roplan, in which chronic illness terminating in cardiac rupture is first described, and continues up to the time (about 1926) when portable electrocardiographs made it possible to confirm the diagnosis in a large proportion of the cases with milder sequelae of coronary occlusion The next phase, of overdiagnosis and overtreatment with dietary prophylaxis, lasted about three decades The year 1955 stands out because two series of cases published that year proved that the classic six-week bed rest had raised mortality, perhaps even doubled it, and even the most conservative authorities in this field began to put their patients on diets low in animal fat and cholesterol Meanwhile, Kinsell, Ahrens, and Bronte-Stewart had proved that in man the intake of saturated fatty acids was probably more important than the cholesterol intake in determining the level of plasma cholesterol

The era just dawning, when illness is managed by physiologic principles and not by custom and when a great decrease in second attacks of coronary disease seems attainable, is fully described in the meticulous treatise to which Milton Plotz has devoted many years of preparation—by study, by discussion with leaders in the field, and by daily practical experience The subject demands a full and up-to-date presentation, and the practicing physician and the beginner in medicine are fortunate to have such a volume as Dr Plotz has given us

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PREFACE

CORONARY ARTERY disease has become the focus of medical and general interest to an extent which no one could have foreseen as recently as a generation ago. It is recognized and properly dreaded in the Western world as the chief destroyer and crippler of men in the years of their greatest economic and social productivity.

Nevertheless, this important affliction is relatively new in the annals of medicine. It is less than two hundred years since Heberden described angina pectoris; it is only in the twentieth century that acute coronary disease has been properly classified and diagnosed Still more important, in the last very few years our attitude toward coronary atheroma has undergone a complete change, a change in concept so radical that a condition long regarded with hopelessness and resignation is now approached with the feeling that we may soon know its cause and possibly its cure Instead of thinking of coronary sclerosis as an inevitable part of aging, an unremitting attribute of senescence, we now see it as a *disease*, probably a metabolic disease, that is, like other diseases, susceptible of study with regard to cause, pathogenesis, treatment, and possibly prevention From indisputable evidence in animals, coronary atheroma in its early stages is reversible, and we hope it will prove so in man. In any case, as physicians and investigators we are willingly compelled to face the problems of this disease in the same way that we have done with other illnesses but now with hope and confidence.

This philosophy, which lies behind this monograph, is rapidly leaving the realm of controversy. But no book on this subject could possibly be written today which would not touch off heated, even bitter, dispute on some points Such matters as the effect of diet and tobacco on the arteries of the heart, the use of anticoagulants and other drugs, etc , are among such topics. In all of these, I have presented varying opinions as fairly as I could but have not hesitated to make my own attitude and practice as clear as possible

Since this is the first full-scale consideration of coronary disease in English in some years, it is addressed to both general practitioners and specialists Diagnosis and treatment of coronary atheromatosis and its more common complications are described as well as some problems less frequently encountered To shorten an already long volume, most of the material on anatomy and physiology, of little interest to the practicing physician, has been omitted, but suitable references are indicated. I regret that I must forego, too, a section on the fascinating but necessarily incomplete history of this disease.

The first chapter, Basic Principles, introduces the subject by means of line

drawings which illustrate current concepts of the coronary circulation as they relate to human disease. The next four chapters are given to a full discussion of the statistics of coronary disease and its causative factors as now understood. The discussion of tobacco occupies a separate chapter in order to limit the length of the chapter on etiology and to reflect the popular interest now being evidenced in this possible etiologic agent. Chapter 6 comprises an exploration of important aspects of pathology and pathogenesis. The seventh, eighth, and ninth chapters constitute a comprehensive discussion of the clinical aspects of coronary artery disease, including its complications The section on electrocardiography is a full one but does not replace material which is to be found in texts devoted entirely to this subject The following chapter contains case reports selected to illustrate not only problems in cardiographic diagnosis but also other interesting aspects of coronary disease The twelfth chapter is devoted to diagnostic methods, as yet not widely employed, which seem useful and likely to become more popular The next two chapters treat the ever-present problems of differential diagnosis and prognosis. The six chapters, from 15 to 20, comprise a section on treatment which embodies all those aspects of therapy which I consider worthy of mention. In some instances, modes of treatment of which I do not fully approve are mentioned because of their entrenchment in modern practice up to now. Prevention has a separate chapter in line with the spirit mentioned in earlier paragraphs of this introduction The increasingly difficult and complex medicolegal aspects of coronary disease are discussed in full in the last chapter

The preparation of this volume was aided by the advice, help, and influence of many people I have profited from my position as attending physician for many years at the Kings County Hospital where Dr Tasker Howard and Dr J Hamilton Crawford encouraged a lively interest in cardiac disease I am indebted to Drs Felix Wróblewski, Alvin Bakst, Howard Eder, Murray Weiner, Paul Weil, and Bernard I. Heller for advice on some chapters, to Drs A Loomis Bell and Theodore Kamholtz for putting x-ray films at my disposal, to Mr Henry L Bayles and Mr. A. Bertram Roth of the New York Bar and Mr Nathan Rabinowitz of the New Jersey Bar for reviewing the section on medicolegal problems; to Mr Herbert H Marks of the Metropolitan Life Insurance Company for kind assistance in preparing the section on statistics, to the Royal College of Physicians for permission to reproduce the portrait of William Heberden used as the frontispiece; and above all to Dr William Dock for constant help and encouragement I am grateful to my secretary, Miss Ethel Ross, for self-sacrificing assistance and to Mrs. Patricia Echevarria and Mrs Pearl Mark for other secretarial help I owe special thanks to Mrs. Natalie Friedheim who, when I thought I had a completed manuscript, skilfully and tactfully took over the many details of preparing it for publication.

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CHAPTER 1

Basic Principles

CARDIAC BLOOD SUPPLY

UNLESS CERTAIN basic priciples are clearly understood, the study of the coronary circulation and its diseases must indeed be incomplete In almost no other branch of medicine do accurate diagnosis and reasonable treatment so depend on the unequivocal knowledge of the changes from good health to disease Consideration of these basic principles may serve to clarify the ambiguity of nomenclature which so confuses and bewilders the physician

The heart, like any other muscle, depends on its own blood supply—the coronary arteries (Fig 1) Except in unusual circumstances, the heart is not nourished to any great extent by the blood within its chambers which it pumps out to the rest of the body When its blood supply is completely cut off, the heart tissue, like any other, inevitably dies

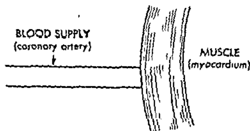


FIG 1 Blood supply to a heart muscle *

The blood in the coronary arteries, like any liquid in a pipe, depends on the force of a pump for motion. The systolic pressure in the main coronary arteries is the same as that in the root of the aorta (Fig 2) The pressure in the coronary artery may be represented as illustrated in Figure 3*A*. With moderate increase in the head pressure, the coronary flow *remains* largely unchanged (Fig 3*C*). With moderate decrease in head pressure, the coronary flow is unimpaired, but with sufficiently low head pressure, the coronary flow may fall off (Fig 3*B*)

Under most circumstances, the coronary circulation adequately meets the demands of the heart But under certain conditions, such as lack of nutritive power or force of flow of the blood, the circulation may no longer be adequate even when the arteries are normal Deficient nutritive power may occur in anemia, in any condition causing insufficient oxygenation of the arterial blood, or in conditions causing lack of sugar or other blood nutrients (Fig 4). Insufficient force may be due to a drop in head pressure to levels too low for an adequate blood flow to the muscle, such as occurs when there is a drop in the aortic blood pressure (*see* Fig 3*B*) Ordinarily, compensatory mechanisms restore adequate blood flow, but if the vessel is not completely patent the heart muscle may suffer damage

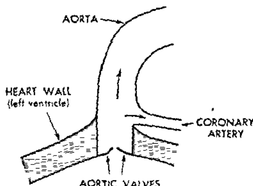


FIG 2 Origin of coronary artery

* All the figures in Chapter 1 except the last are schematic and are not intended to be exact representations

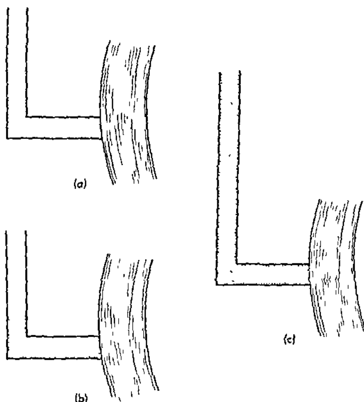


FIG 3 Pressure in coronary artery a, Normal, b, decreased, c, increased

In some cases in which the demands of the heart muscle are excessive, the coronary circulation may be insufficient despite normal blood quality, normal pressure, and normal arterial patency Ordinarily, extra work by the heart muscle which increases its demands for oxygen and nutrients, as in vigorous exercise, hyperthyroidism, or any rise in heart rate, is accompanied by an augmented coronary flow to meet the demand (Fig 5 *A–B*). But when the amount of additional work or the demand for additional blood is too great or prolonged, the coronary flow, though increased, may be insufficient to meet the demand (Fig. 5*C*) Such a situation is rarely important when the heart is normal, but may be harmful in cases in which atheroma has diminished the blood flow, although it is still adequate under resting conditions. Under conditions of extra demand, the increase in blood flow may then be too slight to provide enough blood (Fig 6*A*). Finally, the demands of a hypertrophied heart, as in hypertensive heart disease, may, at least in theory, exceed the capacity of the coronary vessels to supply it adequately (Fig 6*B*).

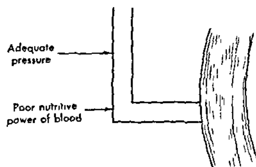


FIG 4 Effect on heart muscle of blood deficient in nutritive power

The most frequent cause of impaired blood flow to the heart is narrowing of the arterial lumen due to (*1*) spasm (Fig. 7*A*); (*2*) obstruction of the arterial orifice, as in syphilitic involvement of the coronary artery (Fig 7*B*); (*3*) obstruction by an embolus, which usually occurs in bacterial endocarditis (Fig 7*C*); and (*4*) thickening of the arterial wall, by far the most important cause of a reduced coronary flow and in the

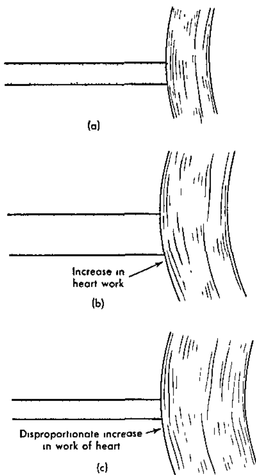


FIG 5 Response of coronary flow to cardiac demand for blood a, Heart at rest, b, heart at work, c, disproportion between demand and supply

vast majority of cases the result of atheroma (*see* Fig 6*A*)

Normally, the intima of the coronary wall is very thin (Fig 8*A*) The atheroma may be simply an intimal plaque projecting somewhat into the lumen of the vessel, the media over the atheroma is thinned, and the atheroma, unlike the intima, contains blood vessels (Fig 8*B*) Or, the atheroma may form a ring around the vessel The width of the lumen may be unimpaired or even widened in the presence of atheroma, in which case the circulation is not impaired On the other hand, the lumen may be reduced, usually eccentrically (Fig 8*C*)

A moderate reduction in the caliber of the lumen may have no harmful effects When the coronary flow falls below a critical level, however, the heart does not receive sufficient nourishment (ischemia) and suffers temporary or permanent damage. Changes within the coronary walls do not themselves produce symptoms or signs, such as electrocardiographic changes. Only alterations in the heart muscle lead to clinically manifest signs and symptoms. For example, advanced sclerosis may exist without any clinical evidence, while moderate sclerosis accompanied by ischemia will result in symptoms, signs, or both (Fig 9 *A–B*)

A short period of insufficient coronary flow, *i e*, ischemia, will often cause cardiac pain (angina pectoris) With a return of an adequate coronary circulation, the pain ceases However, there is a strong likelihood that the heart muscle suffers some permanent impairment after each episode of pain, especially if prolonged or repeated often enough

Sudden, complete block of a main coronary artery may cause the death (infarction) of the affected heart muscle (Fig 10) Gradual or intermittent occlusion may be accompanied by gradual death of heart mus-

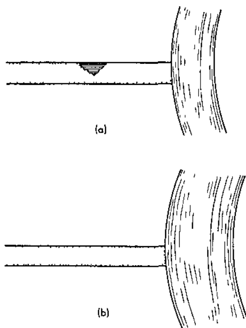


FIG 6 Coronary flow inadequate for cardiac demands a, Coronary flow diminished by atheroma, b, normal coronary artery, but excessive demand by hypertrophied heart

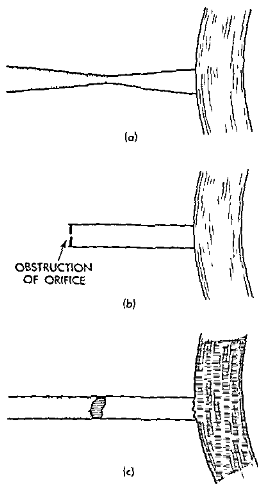


FIG 7 Causes of impaired blood flow in coronary artery a, Spasm b, obstructed arterial orifice, c, obstruction by embolus

cle, with replacement by fibrous tissue (Fig 11)

In many cases of infarction resulting from incomplete arterial obstruction, only the portions most distant from the main artery may be affected (Fig 12*A*) Thus, only the subendocardial layers, rather than the entire thickness of muscle may be infarcted, and in such cases the necrosis is usually patchy. Subendocardial necrosis (Fig 12*B*) occurs most often in the left ventricle (*a*), the posterior papillary muscle (*b*), and the left side of the interventricular septum (*c*) The right ventricle (*d*) is seldom involved in such changes.

Normally, a collateral circulation is of small consequence, but in gradual occlusion of a coronary artery or one of its main branches the development and role of such a circulation are most important. The blood supplied by collateral vessels may be a decisive factor in preventing the death of the heart muscle. The collateral vessels may arise from (*1*) a nonoccluded branch of the same main artery (Fig 13*A*); (*2*) another main coronary artery (Fig. 13*B*); (*3*) extracardiac vessels (Fig. 13*C*); (*4*) in theory, at least, the heart may derive some nourishment from its own lumen (Fig 13*D*).

The heart muscle may die even when occlusion is incomplete, provided the insufficiency of coronary flow is severe enough or prolonged enough (Fig. 14 *A–F*). This usually occurs when one or more coronary arteries are considerably narrowed by atheroma and the head pressure falls abruptly, as in shock or hemorrhage, or when a collateral vessel on which the muscle is partially dependent becomes occluded or spastic The same may result from partial occlusion of the artery supplying the collateral vessel In rare instances, necrosis of the heart muscle may occur despite the absence of coronary disease.

Typical angina pectoris occurs only if heart disease is present, in the vast majority of cases, impairment of the coronary circulation is the primary disease. The patient with angina pectoris who is not anemic, anoxic, or syphilitic, and who has no valvular disease or cardiac enlargement, is therefore almost certain to have one or more narrowed coronary arteries. Spasm alone seldom causes angina pectoris except in the presence of organic narrowing of a large artery

NATURE OF INFARCT

It should be obvious by now that myocardial changes depend largely on changes in the flow of blood in the coronary arteries For a clear understanding of any clinical situation, however, these changes are best considered separately.

What is the nature of the dead cardiac tissue—the myocardial infarct? Generally, an infarct is thought of as a sudden, catastrophic change in the heart muscle, easily identifiable by such clinical features as pain, fever, and leukocytosis The infarct is regarded as a dense, homogeneous area of necrotic tissue

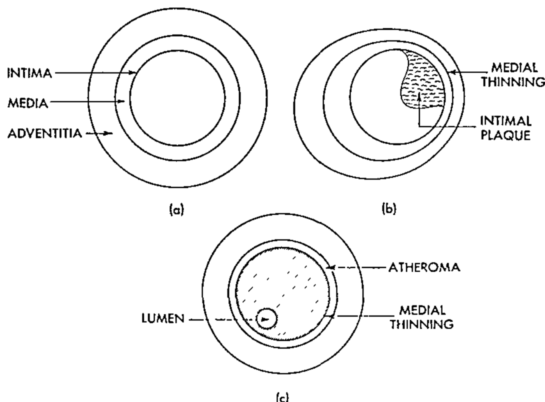


FIG 8 Effect of atheroma on arterial structure a, Normal artery, b, intimal plaque, c, ringlike atheroma narrowing the lumen

with clearly defined borders and extending through the entire thickness of the heart wall (*see* Fig 10) Such infarcts are often called transmural infarcts, to indicate their extent This is too great a simplification. An infarct may be large and disastrous, and yet not be homogeneous or extend from pericardium to endocardium. It may be massive, and yet involve only a fraction of the heart wall thickness. The infarcted area may contain islands of living tissue (Fig 15) The edges of the necrotic area may be irregular, and the boundary between dead and living tissue may be ragged and indefinite The term "major infarct" better describes such infarcts than the term "transmural infarct"

As every pathologist knows, the number of infarcts identified at postmortem examination out-number those clinically recognized by 2 or 3 to 1 Circulatory insufficiency may cause considerable necrosis without any clinical history of coronary disease. This discrepancy is explained in part by the fact that an infarct may develop rapidly or slowly, and that slowly dying heart muscle is replaced by fibrotic tissue (*see* Fig 11). Obviously, not all cardiac fibrosis is the end result of coronary disease, for there are many other conditions which may cause it, but in most instances scar tissue in a heart in the presence of advanced coronary sclerosis, possibly with points of occlusion, is due to slow infarction. The entire process may be clinically imperceptible until there are signs of heart failure or symptoms (especially angina pectoris) arousing suspicion of coronary disease

Another category of infarction, not as dramatic or perhaps as important as major infarction, is nevertheless important with respect to accurate diagnosis and treatment Whether it develops quickly or slowly, the infarct is small—small and circumscribed (Fig. 16*A*), small and patchy (Fig 16*B*), or even entirely intramural (Fig 16*C*) A typical small infarct is illustrated in Figure 17 The infarction may be somewhat more diffuse, so that only a few fibers scattered through a wider area actually die In such

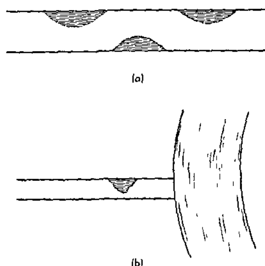


FIG 9 a, Advanced sclerosis in coronary artery, producing no clinical evidence, b, moderate sclerosis with ischemia

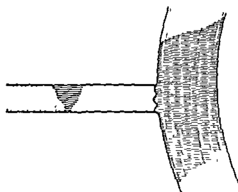


FIG 10 Complete arterial occlusion with myocardial infarction (shaded area)

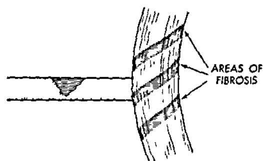
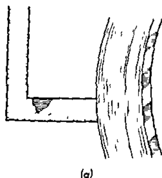


FIG 11 Intermittent occlusion, with myocardial fibrosis



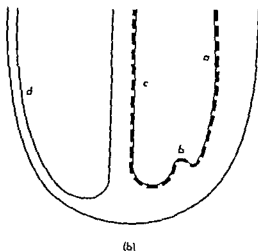


FIG 12 Sites of infarction with incomplete arterial obstruction (a Subendocardial necrosis (b) location of subendocardial necrosis

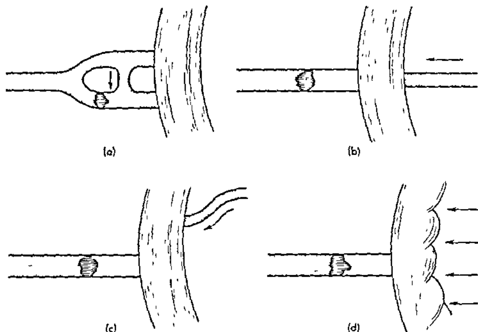


FIG 13 Cardiac blood supply from collateral vessels a, Collateral vessel from unoccluded branch b, collateral vessel from another main artery, c, collateral branch from extracardiac vessel d, from heart cavity

cases, the metabolic function of much of the surrounding muscle may be temporarily impaired but thereafter regain its vitality Finally, there may be patchy areas of subendocardial necrosis (*see* Fig 12*A–B*)

These infarcts, obviously neither massive nor transmural, have long been known to observant clinicians, and are being recognized with increasing frequency They are usually included in such categories as "good risk" cases, but I prefer the term "minor infarction" for this category Often the diagnosis of a minor infarction is easy When cardiac pain is associated with electrocardiographic changes, usually in the S–T and T segments, and there is laboratory evidence of tissue necrosis (fever, leukocytosis, abrupt increase in sedimentation rate, or a positive result of the transaminase test), it is safe to assume the presence of a myocardial infarction

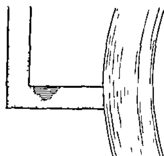
Even in the absence of laboratory evidence of tissue death, some degree of infarction may nevertheless be present, but the diagnosis is then neither as easy nor as sure For example, in a case recently seen, angina pectoris suddenly developed in a man, and T wave inversion in the precordial leads lasted for 3 weeks, it seems highly probable that this was a case of infarction, though not extensive enough to produce laboratory evidence of necrosis When there is no laboratory proof of infarction and the S–T or T wave changes last only a few hours or less, the electrocardiographic changes may be due to a reversible state of circulatory insufficiency, what Master has called coronary insufficiency

SUMMARY

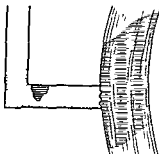
Myocardial infarction may occur slowly and imperceptibly, or more rapidly and with more pronounced signs and symptoms The infarct varies greatly in extent For the sake of convenience, infarcts may be classified as major or minor But despite modern methods of diagnosis and a high index of suspicion, some infarcts will fail to be diagnosed or classified

Certain anatomic and physiologic features that distinguish the coronary circulation from that of other organs have made it difficult to determine the factors controlling the blood flow to the heart

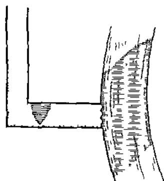
In general, the amount of blood reaching a tissue depends directly upon the pressure



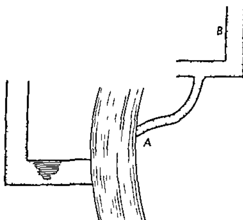
(a)



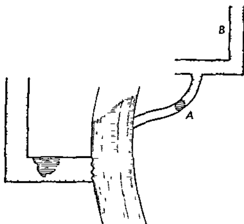
(b)



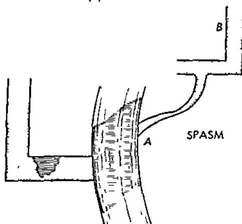
(c)



(d)



(e)



(f)

FIG 14 Infarction with partial occlusion a, Circula-
on impaired but adequate for most purposes; b, fall
head pressure resulting in infarction, c, hemorrhage
atheroma resulting in infarction, d, blood supply in part by collateral vessel (A) from another main artery (B), e, occlusion of collateral vessel (A) resulting in infarction, f, narrowed lumen of collateral vessel due to spasm resulting in infarction



FIG 15 Infarcted muscle with islands of living tissue

of the blood delivered to its capillaries The blood is propelled by ventricular contraction, and the flow is maintained during diastole by the elastic recoil of the arterial walls This forward movement is opposed by the peripheral resistance to flow of the progressively smaller vessels through which the blood must course, and by the viscosity, or internal friction, of the blood itself.

Physiologically, the coronary circulation is unique in that the peripheral resistance to blood flow varies throughout the cardiac cycle as the ventricular muscle contracts and relaxes The flow reaching the cardiac muscle is therefore the resultant of a pulsatile inflow from the aorta, and a pulsatile peripheral resistance

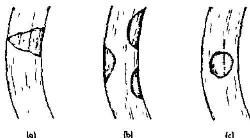


FIG 16 Minor infarction a, Circumscribed b, patchy c, intramural

Differences in the anatomy and physiology of the coronary vessels among various species as well as among individuals of the same species have not been stressed adequately in the literature Relatively few studies have been made of the human coronary circulation because of the obvious difficulties involved Despite this, conclusions with regard to the coronary physiology of man have been drawn freely on the basis of experiments on lower animals Furthermore, knowledge drawn from studies of the isolated, denervated heart has been applied too readily to man The physiology of the coronary circulation has been reviewed critically from different points of view by Wiggers, Anrep, Ratnoff and Plotz, and more recently by Gregg, by Wégria, and in several papers by Bing



FIG 17 Small myocardial scar of infarct resulting from occlusion of small branch of anterior descending coronary artery (From Gould, S E Pathology of the Heart Springfield Ill Thomas 1953

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CHAPTER 2

Etiology and Statistics

INCIDENCE

It is widely thought, at least in the United States, that coronary disease is on the increase This belief I share but with some misgivings Most published statistics inspire no great confidence in such a belief

It is difficult for those whose medical education was acquired in the past decade to realize how recent are the present concepts of coronary disease, and how shifting and tenuous the descriptive nomenclature has been In this country, acute coronary thrombosis has been diagnosed with assurance only since about 1920 In England, the clinical picture of coronary thrombosis was introduced by McNee in 1925. As late as 1923, MacKenzie missed an easy diagnosis of myocardial infarction, and the term "vasomotor angina" was in common use " Up to 50 years ago, what is now known to be chronic coronary disease was not differentiated from "chronic myocarditis", this term even today is found on death certificates to describe a condition which is far from inflammatory in nature There were no official mortality statistics for coronary disease until 1929, when for the first time the *International Classification of Causes of Death* gave "disease of coronary arteries' as a category The 1948 revision lists coronary artery disease in category 420 1, but arteriosclerotic heart disease in 420 0 and angina pectoris in 420 2, leaving room for the perpetuation of error

The textbooks of the late 1930's and early 1940's discussed angina pectoris and coronary disease as though the two were entirely different conditions Vital statistics during this period still listed "deaths from angina pectoris." Terms such as "coronary sclerosis," "coronary narrowing," "coronary occlusion," and "coronary thrombosis" were used vaguely and interchangeably. To this day, one large organization uses "arteriosclerotic heart disease" for coronary disease, possibly with some reason but certainly with a resultant haziness

From an examination and evaluation of the published statistical studies I have concluded that all statistics compiled before 1920 should be discarded, or accepted only with the greatest reserve, although they were honestly collected at the time *Even today, the only* valid statistics are those based on postmortem examination, clinical studies, carefully controlled and based on electrocardiographic examination though they may be, can be accepted only to a limited extent Nor do postmortem figures completely solve the problem of statistical analysis, since the validity of autopsy studies themselves varies with the technics used and with the vagaries of nomenclature What is to be done, for example, with autopsy reports which list a certain number of hearts as having "coronary disease" or "coronary sclerosis" without stating whether the changes were greater or more severe than those occurring in the hearts of presumably normal individuals? How are "coronary narrowing," or "occlusion," or even "myocardial infarction" to be evaluated unless we know their duration or their relation to cause of death? How is "significant coronary sclerosis" to be judged, although this term is less vague than the names previously used? I use "infarction" whenever possible as a term which more accurately describes the significant pathologic process, although I am well aware that death may occur in coronary occlusion without detectable infarction

Another difficulty in assessing published statistics, even those painstakingly gathered and sifted by life insurance companies, is that coronary disease has now become a fashionable diagnosis Coronary occlusion or

myocardial infarction may be found listed as the cause of death in university medical centers merely because the diagnosis was most likely, statistically, to fit a clinical situation. This practice is even more widespread among general practitioners. Sudden death is almost invariably ascribed to "coronary thrombosis," an assumption which every medical examiner knows to be wrong.

Heart disease is now the leading killer in the United States, and within this category coronary artery disease is the most frequent. It is the condition most likely to kill or strike the head of the family, the man between the ages of 40 and 60. It accounted for about 40 per cent of all deaths due to cardiac disease in 1938, at one hospital, it was responsible for 54 per cent of all deaths.[141]

How prevalent is coronary atheroma (coronary sclerosis)? It may be assumed that some sclerosis of the coronary vessels is present in most persons who have passed the age of 40, although not necessarily accompanied by luminal narrowing functional changes. More painstaking studies, with accurate measurements of the type used by Lober,[230] are needed.

How prevalent is coronary sclerosis of sufficient extent or degree to affect the functional capacity of the heart? At one university hospital, narrowing of one or more coronary arteries was found in 1629 out of 3000 hearts examined at autopsy. It is impossible to say in how many of these the function of the cardiac apparatus was impaired, but definite coronary narrowing, no matter in how large a number it may be present, should be regarded as a disease, or at least as an abnormal state. "Significant coronary disease" was found in 25 per cent of 2000 cases examined postmortem.[245] Another report states that 5 per cent of hearts have severe atherosclerosis at some site in the coronary tree by the age of 40, and by the eighth decade about 60 per cent of the coronary arteries are involved—52 per cent of the left coronary arteries and 36 per cent of the right.[1] Severe sclerosis (Grade 3 or more) was found in 18 per cent of hearts in the 30 to 39 year age group, and a similar grade of sclerosis at some point in the coronary circuit in the "average man" over the age of 49.[251] In still another report, 35 per cent of hearts over the age of 35 showed at least one point of complete occlusion, and more often if they fell into the author's Group I, however, only in about half of these cases was coronary disease a major factor in causing death.[202] A pretty distinction which might be adopted more widely has been made between *coronary disease*, in which the arteries alone are affected, and *coronary heart disease*, in which the myocardium is compromised because of changes in its circulation as the result of coronary disease.[62]

How often is myocardial infarction the principal cause of death? Available data do not provide a complete answer, but published statistics in the United States seem to indicate that infarction is present in about 1 heart in every 10 examined at autopsy. Among the reported figures are: 7.8 per cent of 3559 autopsies,[137] 865 unhealed infarcts in a series of 25,000 autopsies in Los Angeles, in a series of autopsies in 1927 2.4 per cent showed infarction,[60] which rose in the following years to 6.7 per cent and between 1941 and 1945 to 14.1 per cent,[243] 147 infarcts (53 acute, 94 old) in a series of 1250 consecutive autopsies,[51] 8.2 per cent of 2000 hearts examined postmortem had infarcts, at the Massachusetts General Hospital, 270 myocardial infarcts (105 recent, 165 healed) were found in 2967 autopsies.[213]

What is the incidence of "coronary attacks" in the United States? An estimate some years ago put the figure at 500,000 attacks a year, about 1 man of every 38 over the age of 40 and 1 woman in 115 are stricken each year.[141] Such estimates, rough as they are, give some idea of the magnitude of the problem. Tables 1 and 2 give the latest available figures. The Metropolitan Life Insurance Company[140] reports a mortality rate from coronary heart disease of 108.7 per 100,000 for 1953 and 104.8 for 1954. This decline in 1954, part of a general drop in cardiovascular and renal diseases in 1954, may perhaps be related to the influenza epidemic in 1953, and the absence of one in 1954, in the company's experience, outbreaks of respiratory disease usually hasten the death of many persons with chronic illnesses.

Statistical studies from other countries are few. British investigators, handicapped by the same limitations as ours, come to about

TABLE 1. Deaths from Disease of the Cardiovascular and Renal Systems, United States, 1949-1953[204]

Disease	*Death rate per 100,000*					*Number of deaths*	
	1953[a]	*1952*[a]	*1951*	*1950*	*1949*	*1953*[a]	*1952*[1]
Cardiovascular system diseases	501.4	495.0	498.3	494.4	484.6	794,120	771,020
Vascular lesions of central nervous system	108.2	108.9	106.6	104.0	100.9	171,410	169,620
Rheumatic fever	0.9	1.0	1.1	1.3	1.5	1,490	1,620
Heart diseases	357.6	351.3	355.8	355.5	348.8	566,420	547,280
Chronic rheumatic heart disease	12.1	12.5	13.0	13.5	13.7	19,120	19,410
Arteriosclerotic heart disease, incl. coronary disease	233.6	222.5	219.5	213.0	201.2	370,000	346,590
Nonrheumatic chronic endocarditis and other myocardial degeneration	46.3	48.4	52.6	56.5	61.5	73,280	75,340
Other heart diseases	14.6	14.9	15.1	15.9	16.0	23,160	23,180
Hypertension with heart disease	51.1	53.1	55.6	56.5	56.4	80,860	82,760
Hypertension without mention of heart	7.9	8.2	8.6	8.3	8.2	12,520	12,810
General arteriosclerosis	20.7	20.0	20.8	20.4	20.5	32,830	31,170
Other circulatory system diseases	6.0	5.5	5.4	4.9	4.7	9,450	8,520
Chronic and unspecified nephritis and other renal sclerosis	12.0	13.5	14.7	16.4	17.4	18,990	20,980
Total cardiovascular renal diseases	513.4	508.5	513.0	510.8	502.1	813,110	792,000

[a] Estimate based on a 10 per cent sample of the death certificates received in State Vital Statistic Offices

TABLE 2. MORTALITY RATES, WHITE PERSONS, FROM HEART DISEASE, 1950-1952[a] [130]

	Males		Females	
Age in years	*Total heart disease*	*Arterio-sclerotic, including coronary*	*Total heart disease*	*Arterio-sclerotic, including coronary*
AVERAGE ANNUAL DEATH RATES PER 100,000				
1–74[b]	343.3	240.3	171 2	95 5
1–4	4 7	0 1	5 5	0 1
5–14	3 9	0 1	3 5	0.1
15–24	8 4	0 8	7 0	0 5
25–34	29 4	10 3	15 5	2.1
35–44	140 4	88 0	47.9	14 3
45–54	499 3	365 4	164 0	76 4
55–64	1,176.7	870.7	511 3	305 0
65–74	2,492 9	1,719 3	1,574 3	947.6
PERCENTAGE OF TOTAL HEART DISEASE				
1–74	100 0	70 0	100 0	56 2
1–4	100 0	1.2	100 0	1 0
5–14	100 0	2 1	100 0	2 3
15–24	100 0	9 4	100 0	6 9
25–34	100 0	35 0	100 0	13 7
35–44	100 0	62.7	100 0	29 8
45–54	100 0	73 2	100 0	46 6
55–64	100 0	74 0	100 0	59.7
65–74	100 0	69 0	100 0	60 2

[a] Congenital and syphilitic heart disease, and rheumatic fever, are included in this study.

[b] Adjusted for age on basis of total United States population, 1950

the same conclusions as we do. In Australia, the death rate from coronary occlusion rose from 11 per 1000 between 1920 and 1925 to 45 per 1000 between 1943 and 1946, the rise is greater than can be explained on the grounds of aging of the population or of better postmortem diagnosis.[53] Such figures and conclusions, too, although gathered conscientiously, must be viewed with reserve, for the same reasons as apply to figures in our country.

As has already been noted, changing fashions in diagnosis constitute one source of error in evaluating statistics on heart disease Another source of error is the gradual increase in the age level of the American population. As death from some causes, especially infectious diseases, is successfully evaded, life expectancy rises, and the age group (over 60 years) in which arterial disease may be expected to be a greater factor grows larger. To conclude that coronary disease is more prevalent than formerly, the data would have to be broken down into age groups, and the diagnostic methods would have to be comparable. Only a limited number of such statistical studies of sufficiently large series are as yet available The feeling which most of us have that coronary disease is genuinely on the increase is still largely an article of faith. An excellently studied series in Chicago indicates that there has been little or no change in the frequency of coronary heart disease in the past 34 years but that there has been a striking increase in incidence in persons below the age of 50.[201a] Lee and Thomas have found a great increase in the incidence of coronary disease at the Barnes Hospital of St. Louis in the past three decades; they wonder if increases in smoking and dairy fat ingestion are responsible.[123a]

SUDDEN DEATH

Coronary disease, especially coronary thrombosis, is not the commonest cause of sudden and unexpected death, as may be clearly seen from available statistics [110, 124, 249] These show that cardiac and aortic disease account for less than half of the sudden deaths.

In the experience of the New York Medical Examiner's Office, 44 9 per cent were due to cardiac disease, and about two thirds of these (30 4 per cent of the total) were coronary artery disease [110] The numerous other causes of sudden and unexpected death are listed in detail by Gonzales and associates.[92] Of course, the percentage of the deaths due to coronary disease might be higher were autopsies performed more frequently in the case of sudden death of older individuals (Fig 18). Only in 25 per cent of the coronary cases were fresh thromboses found In a fourth of them there was no infarction, either because an effective collateral circulation was present, or, a more likely reason, because the patient had died before myocardial infarction could occur Of the three fourths with fresh infarction, antecedent fibrosis could be seen only in half. Advanced occlusive coronary disease was found in 75

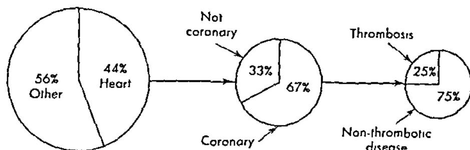


FIG 18 Causes of sudden death

per cent of the cases with coronary disease (i e, of the 30 4 per cent of the total), but there was no evidence of fresh clots Of this group, 50 per cent had myocardial fibrosis and another 5 per cent myocardial infarction In such hearts, with coronary flow already reduced, unaccustomed exertion or emotion may increase the myocardial demands on the circulation beyond the critical point In the presence of such acute coronary insufficiency, ventricular fibrillation or asystole may stop the heart abruptly [92]

Gonzales and associates go a step further and say "Occasionally even a normal heart with intact coronary circulation and myocardium may stop suddenly because of an unusual strain brought about by severe physical effort" They cite the case of a 17-year-old boy who swam 15 feet underwater in a race, after completing it, he was able to lift himself out of the pool to the ledge, where he collapsed and died Autopsy revealed a dilated heart of normal weight without evidence of coronary, myocardial, or valvular disease In this case, it was concluded that the combination of anoxia, severe physical exertion, increased heart action, and the inability of the coronary arteries to deliver normally oxygenated blood to the myocardium resulted in sudden cardiac death Others, too, have noted similar instances. The explanation given by Gonzales and associates may well be correct, nevertheless, it is not the only possible one. Other organs and other mechanisms may be involved

ETIOLOGIC FACTORS

FAMILIAL FACTOR

There are apparently good reasons for believing that coronary disease is in many cases familial Four times as many cases of cardiovascular disease were found in the immediate families of one series of patients as in a control group [269] In another series, 45 per cent of the patients had a family history of heart disease.[22] Other reports also point in the same direction [51, 185]

Especially convincing evidence is provided by a study of the families of a series of 100 young adult patients [54] 37.1 per cent of the fathers had died from coronary disease, as compared to 18 5 per cent in a group of controls; the figures for siblings were 8.6 per cent for siblings of the patients, and 1 per cent for the controls The evidence was against the inheritance of coronary disease as a dominant or a recessive simple mode, but pointed to familial transmission, possibly to a multiple-factor condition with at least one dominant factor The younger the patient, the more likely was a positive family history

There are several possible explanations of the familial incidence of coronary disease (1) The patterns of coronary architecture may be familial (2) There may be inherited differences in the structure of the coronary intima (3) There is impressive evidence of familial patterns in lipid metabolism, noticeable even among elderly patients (4) The body habitus (somatotype) is probably genetically determined (5) Other familial factors than genetic ones may play a role, e.g, eating and smoking habits, living conditions, psychic habitus, or occupation.

AGE FACTOR

The incidence of coronary disease is a function of advancing age: the older the individual, the more likely is the presence of coronary disease. Correlation between coronary artery changes and aging may be identified almost from birth, and this in-

creases with age.[102, 130] In addition, atheromatous changes which should be considered pathologic occur with increasing frequency in each successive age group

The adult type of atheroma may be found at any age, although rare, it has been reported in children and young adults under the age of 20 (The medial calcification in infants, which is somewhat more common, is not of concern at this point) The histologic features and involutionary features are about the same at all ages, except that in the younger patients there may be somewhat greater fibrous intimal proliferation and somewhat less calcification. Furthermore, in these patients, the earlier the coronary disease appears the more apt is it to be an isolated lesion without associated arteriosclerosis elsewhere [2] The fatal lesion in young individuals may consist only of a small plaque in a single coronary artery, every other vessel (including the other coronary arteries) remaining supple and free of any trace of disease [52]

The age-specific morbidity rate (number of cases related to total number of living persons in the age group) cannot be given exactly, it may be inferred, however, from the available figures for the ages at which myocardial infarction is noted and the ages at death. The mean age for first attacks (presumably of major myocardial infarction) is about 59 or 60, various reports give it as 60 (58 for men, 64 for women),[22] 58.7,[194] 59,[193] 60 4,[156] 57 for men, and 53 for women, with more than one third of the patients suffering the first symptoms between the ages of 50 and 59 [207] The last report cited states that the decade between 60 and 69 was the next in frequency, and the one between 40 and 49 the third most frequent In one interesting series, the incidence of coronary attacks in men reached a high peak at age 55 to 59, and then fell sharply, in women, the rise was slow and steady from age 40 to 70, without the drop noted in men [176] The incidence seems to decrease slightly in the very aged, this is probably due to the survival of a few individuals with remarkable hearts [130] Nonetheless, classic coronary disease, with all its attendant changes is found even in extremely old persons, and one report describes 9 patients over the age of 100.[104]

The average age at death, according to one study, is 61 5 (60 9 for men, 62.9 for women) [137] Table 2, which shows the experience of the Metropolitan Life Insurance Company,[170] gives evidence of the steep rise in mortality rates with advancing age, this is also borne out by all published figures for all types of individuals and both sexes

PREMATURE AGING

It has been suggested that arcus senilis is found more frequently in patients with coronary disease and that its incidence increase with hypercholesterolemia,[26, 27] but other investigators have challenged this suggestion,[79] among 100 young adult patients, only 5 had an arcus senilis, and their serum cholesterol content averaged 275 mg per 100 cc [84]

Young patients with coronary disease often appear a decade older than their chronologic age Mesomorphs, in general, seem prematurely aged, partly because of the coarse, heavy wrinkling of their skin, they also reach puberty 1 to 1½ years earlier than other children. Gertler and White conclude "It is reasonable to suggest that mesomorphs at all ages are physically 10% older than their chronological age " This provocative thought deserves further investigation

Many clinicians, myself included, have thought that young patients with coronary disease have gray hair or are bald more often than is the case among young people generally Gertler and White did not find this to be true in their study However, of the last 30 patients under the age of 45 whom I have seen, 25 were either noticeably bald or gray, it would therefore seem that this is still an open question. Since baldness, in addition to being a function of masculinity and genetic factors, is also one of advancing (not advanced) years, it may be that individuals subject to coronary sclerosis "live faster" than others

RACE

For a discussion of the racial and geographic factors in coronary disease, see Chapter 3

SEX

Many aspects of coronary disease are controversial, but no one disputes the fact that it is dominantly a disease of the male sex. In youth, the patients are overwhelmingly men; this predominance begins to disappear in older age groups, and in old age both sexes are equally vulnerable Disregarding age, the ratio of men to women, as given in clinical reports ranges between 5 to 3[37] and 13 to 1,[173] a summary of the data given for seven carefully studied series yields a ratio of 4 to 1 (1716 men, 429 women)

The male preponderance is modified by advancing age, up to the age of 40, men far outnumber women, in one series of 100 patients only 3 were women,[94] in another, of 88 patients, the only woman under the age of 55 had had a bilateral oophorectomy at the age of 18[115] The figures in old age are quite different in one series of 100 cases studied at autopsy, 11 of 16 nondiabetic women were 70 years or over,[42] in another series, 65 per cent of all the men were over 50, but 86 per cent of all the woman, with the average age of known onset being 53 3 for the men and 58 9 for the women,[1-6] in a third series, the ages at onset were 58 4 and 62 4, respectively[150]

We cannot readily explain why the male of the species is more vulnerable to coronary disease than the female In certain animal species, spontaneous arterial disease is much more frequent in the male than in the female Although there is some evidence that in man the intima of the male coronary artery is thicker at birth than that of the female,[62] the number of cases on which this is based is still too small for conclusions to be reached

Other theories about the relative immunity of the female include a different and possibly better lipid metabolism, less muscular work, smaller ventricular mass, periodic blood loss, lower normal hematocrit level and blood viscosity, arteriolar dilatation at the menses, and vascular changes at the menses.[115]

A number of factors may accelerate or favor the occurence of coronary disease in women; among these are diabetes, hypertension, obesity, and surgical castration. Thus, coronary disease develops more often and at an earlier age in women with diabetes than in nondiabetic women. In one series of 87 female patients, 84 per cent had hypertension;[223] in another series, 49.4 per cent had antecedent hypertension (in contrast to 29.7 per cent of the male patients);[150] in a third series, diabetes and/or hypertension were found in over 90 per cent of premenopausal women and in 70 per cent of postmenopausal women with coronary disease.[114] The statistical evidence about obesity, which is commonly held to be an accelerating factor in women, is equivocal; in one series, 64.6 per cent were obese[114] Coronary atheroma may occur at an earlier age in women who have undergone surgical castration.[207] It has been stated that the lower the social class, the more likely are women to have coronary disease[100] The significance of this finding is obscure, possibly, medical advice is sought later by the economically depressed.

The female mortality rate from coronary disease is usually higher than that of the male[150, 203] 45 3 per cent for women and 37 1 per cent for men in one reported series.[10] This difference may be largely ascribed to the fact that coronary disease usually strikes women at a later age than men and that women more usually suffer from complicating disease, such as diabetes or hypertension.

Anatomic coronary atheromatosis, as distinguished from clinically evident disease, occurs almost as often in women as in men, the process appears later in women, the involvement in women in their sixth decade being of about the same extent as in men in their fourth decade However, the atheromatosis in men is usually more severe. According to Barr,[13] who has summarized all the evidence, the involvement in women increases steadily with age, nor is there any indication of sudden increase with the menopause Neither, however, is there any clear-cut evidence for assuming that the menopause is without influence. Even in the fourth decade, the involvement in women is 70 per cent or more of that in men Obviously, the pronounced sex difference is in the incidence of clinically evident disease rather than in anatomic involvement of the coronary arteries

WEIGHT AND BODY BUILD

Obesity or overweight is considered by many to play an important role in the occurrence of atheromatosis. For example, one report states that there is a "statistically significant relationship between obesity and atherosclerosis,"[152] and another that "in our present state of knowledge the prevention and correction of obesity is the most plausible treatment of atherosclerosis."[241] In one series of cases of infarction proved at autopsy, 23 per cent were obese.[135] Other reports state, one third of the patients with coronary disease were obese;[22] 28.1 per cent of the men and 52.6 per cent of the women were overweight,[213] 87 per cent of a series of 77 women patients were obese,[91] in a series of 80 fatal cases under the age of 34, 73 were overweight,[73] 49 of 108 patients were obese,[71] 35 per cent of another series were obese,[212] in two series of young patients, the majority were obese [42, 89] A number of investigators have concluded that obesity is more common in sufferers from coronary disease than in the general population,[115] or that obesity predisposes to coronary sclerosis [115, 257] From published figures, it would seem that overweight plays a more important role in women than in men, the contrary opinion has been expressed by some observers [1, 115]

Experimental atherosclerosis was more easily induced in heavier rabbits than in the lighter ones [151]

Leanness, as such, according to some, has its reward in a relative immunity to atheroma,[1, 206] however, when atheroma does occur in the underweight, the mortality rate is *apt to be higher* [22, 213]

The role of the blood lipids in obesity is discussed in Chapter 4.

The theory that obesity is a predisposing factor in coronary disease has been seriously questioned in recent years The causal relation of obesity to coronary disease is doubted by Ryle and Russell,[199] although they grant that it may add an extra load to a heart which is compromised; only 3 per cent of their male patients and 9 per cent of their female patients were obese Other investigators have not found any correlation between body weight and atheroma,[217] or that obesity is an important causative factor,[154, 299] or that obesity has any effect on atherosclerosis if hypertension and age are ruled out.[61]

Gertler and White, who made an intensive study of the problem of coronary heart disease in the young adult, concluded that the 100 patients in their investigation (97 men, 3 women) were not overweight as compared to a control group Using the Sheldon system for classifying physique, they found a significant correlation between coronary disease and a particular body build or habitus—the endomorphic mesomorph—rather than with body weight The mesomorph is a fat, muscular person, in contrast to the ectomorph, who is a long, lean individual (not necessarily an emaciated one) A coronary ailment, according to Gertler and White, is least likely in the ectomorph, the few in their series with coronary disease had some mesomorphic characteristics In general, the group with coronary disease exhibited the following characteristics (*1*) decreased vertical measurements—stature, span, and total face, hand, and chest lengths; (*2*) increased horizontal measurements—hand and nose breadths, and (*3*) increased depth measurements—upper chest and total chest depths Evidence confirming the findings of Gertler and White may be found in the autopsy studies of Spain and co-workers [217] They found a high degree of correlation between mesomorphism, elevated serum B-lipoproteins, and coronary disease

As can be seen, the various reports raise as many questions as they answer. What is obesity? Is it the same as overweight? What norms are being used? Are the people of the *United States, as a group, overweight? Do* common factors—genetic, neural, and other—produce both obesity and atheroma? Are there common metabolic faults? Do occupational factors predispose to both conditions? Does obesity act by overtaxing a diseased heart? Does correction of overweight beneficially affect existing atheroma? Is the important factor a reduction in total calories consumed, or the elimination or reduction of some specific dietary fraction, such as fat? Is excessive weight in women, who are subject to atheroma at a later age than men, an important causative factor? What relation, if any, has overweight to the develop-

ment, or speed of development, of coronary disease in any one individual, even granting that genetically determined habitus is more important?

Until questions such as these are answered, the best advice to give our patients, and the coronary-disposed public in general, is to avoid overweight In the young male, obesity probably does not contribute much to the genesis of coronary disease, in older men, and in women, its importance seems somewhat greater The mere process of weight loss may reduce the lipoprotein and cholesterol contents of the blood, should these lipid fractions prove to be causative in atheroma, we would be provided with a most persuasive argument for weight reduction

OCCUPATION

Much that has been written about the association of certain occupations and coronary disease may be true, but it has largely been based on clinical impressions rather than on a sound statistical foundation The problem has two aspects: (*1*) Are coronary-susceptible individuals apt to choose particular occupations? (*2*) Does the nature of certain occupations increase the risk of coronary disease?

TABLE 3 ESTIMATED MEAN ANNUAL DEATH RATE PER 100,000 FOR VARIOUS CATEGORIES, 1933-1937

Group	*Age* (*yr*)			*Totals*
	35–44	45–54	55–64	
a	47	109	475	154
b	37	150	304	140
c	36	147	357	128
d	29	124	253	107

A few studies and some official statistics provide data which in part answer the questions In a study[100] of deaths from coronary occlusion among white men in Philadelphia between the years 1933 and 1937, the total figures were separated into four categories: Group *a*, professional men, Group *b*, proprietors, managers, and officials, Group *c*, clerks and salesmen, and Group *d*, workers, the results are shown in Table 3 The standardized mortality ratio* for arteriosclerotic (coronary) heart disease for men in England and Wales, for the year 1951, grouped according to occupation are:[95]

Group	*Standardized mortality ratio*
I	150
II	110
III	104
IV	79
V	89

Group I includes professional and similar pursuits, Group II represents intermediate occupations, such as that of farmers; Group III, skilled workers, *e g.*, transport workers, clerical workers, armed forces; Group IV, partly skilled workers, such as mine and agricultural workers, and Group V, unskilled laborers, such as building and dock workers

The most recent study is a statistical analysis of coronary disease among the employees of the London Transport Executive during 1949 and 1950[160] The incidence and case-fatality rates among the more sedentary workers—drivers, telephone operators, executives, and clerks—were higher than among the employees doing work requiring greater physical activity—conductors of buses and trams and letter carriers These findings were tested in three ways (*1*) The analysis was repeated for the years 1951 and 1952, the results obtained were the same as for the previous years (*2*) An analysis of the Registrar General's mortality figures for coronary disease and for occupations, 1930-1932, supported the hypothesis that, during middle age, mortality from coronary disease as a whole is lower among workers in occupations calling for heavy physical effort than among those whose work is light (*3*) A 2-week sampling of the death certificates of all men between the ages of 45 and 74 reported as dying from coronary disease showed that a smaller number of men whose occupation was classified as "heavy" died in the first attack than of those listed as "light" workers The investigators interpreted these data as supporting their provisional hypothesis. "Men in physically active jobs have a lower incidence of

* Number of deaths among men in a given group expressed as a percentage of the number of deaths that might have been expected in a standard population of the same sex and age.

coronary heart disease in middle age than have men in physically inactive jobs More important, the disease is not so severe in physically active workers, tending to present first in them as angina pectoris and other relatively benign forms, and to have a smaller early case-fatality and lower early mortality-rate." Paul White,[212] too, states: "One has the definite impression that it is distinctly less common in the lean laborer or farmer."

Gertler and White found that coronary disease in their young adult patients, most of whom were city dwellers, was not confined to any one occupational class but that the incidence was relatively higher among those in managerial and executive positions. Other reports state that 67 per cent of the patients were business executives or men in small businesses requiring great individual effort and initiative,[212] and that the lowest rates were found among coal miners and quarry workers, agricultural and chemical workers [193]

Economic factors have been proposed by some. for example, coronary disease disproportionately affects the rich (a widely held theory),[36] the incidence is much higher in private patients than in those in hospital wards,[93] citation of mortality rate figures to show the higher incidence of coronary disease in the more favored economic groups [173]

Physicians have long insisted, rather wryly, that coronary atheroma is the "doctor's disease" Some trustworthy statistical studies would seem to substantiate this idea,[56 159 199] while others cast doubt on the thesis.[125 143] Surgeons, obstetricians, and gynecologists are reportedly even more vulnerable than other members of the medical profession [56] It seems more probable that physicians share the special susceptibility, whatever the cause may be, of those generally classified as managers and executives

Some have challenged the hypothesis that coronary disease has a predilection for certain occupations;[115 145 188] in one study, the high incidence of "working class" patients was found to be mainly in one ethnic group (Jewish) [27]

That the variety of opinions creates confusion is hardly surprising Both statistics and inferences are open to question, and the only thing that may safely be concluded is that coronary disease seems to occur somewhat less often among manual workers

A number of questions need to be answered:

1. In what way does physical activity, as such, reduce the tendency to atheroma, if it does? Does it operate by inducing weight loss, or by providing an outlet for aggressive feelings which otherwise might be harmful? Does spasmodic, and sometimes excessive exercise, such as weekend golf, tennis, or handball, affect the arteries adversely [20]

2. Do certain occupations generate emotional tensions that may be physically harmful? Although it has been suggested that coronary disease is "peculiarly associated with high pressure intellectual activity"[176] it seems unlikely that intellectual activity, in itself, would affect the human organism in this way.

3 Is it possible that the men who choose lighter work for reasons of health could affect the vital statistics to an appreciable degree? This aspect has been largely ignored, yet in any industry there is always a certain amount of such transfer

4 Should data based on occupation be weighted for such factors as sex, race, and urban versus rural living? Few statistical studies have taken any of these factors into consideration

5 Is is not possible that the apparent correlation of occupation with coronary disease is actually a correlation with dietary habits in different economic and social groups?

Gertler and White have sensibly suggested that the choice of occupation may depend on the individual's somatotype Mesomorphy is associated with a driving temperament, which in turn dictates the way a person lives

A reasonable conclusion would seem to be that coronary disease is somewhat loosely, but definitely, associated with certain occupations Most of the evidence apparently points to the explanation that individuals of a particular temperament seek certain work rather than that factors connected with the work itself accentuate "coronary susceptibility"

ROLE OF OTHER DISEASES

HYPERTENSION. An important role in the etiology of coronary heart disease seems to be played by hypertension, and statistical studies on the whole indicate this clearly There is a wide spread in the figures given,

depending on the source material used and the definitions of hypertension and coronary disease. The common assumption that cardiac enlargement necessarily means antecedent hypertension is fallacious,[167] while it may often be the case, there are other causes of hypertrophy. However, hypertension is without doubt frequently found in patients with coronary disease, and indeed has even been described as the most important cause. The interesting suggestion has been made that the reduced coronary flow resulting from coronary sclerosis may lead to hypertension as a means of increasing the head pressure in the coronary arteries.[269]

Published data have been interpreted as indicating that hypertension precedes coronary occlusion in 25 to 75 per cent of cases, as compared to a hypertension incidence rate of 2 to 11 per cent in the general population.[53] Other figures are: (*1*) Hypertension is found 3.4 times as often in those with coronary disease as among otherwise normal individuals.[45] (*2*) There is some degree of coronary sclerosis in 90 per cent of hearts of those dying with hypertension, and antecedent hypertension in 75 per cent of all patients with coronary disease.[64] (*3*) Hypertension was present in 46 per cent of cases cited in the literature.[54] (*4*) Antecedent hypertension was found in 61 per cent,[270] in 58 per cent,[215] in 57.9 per cent,[97] in 54 per cent,[22] and in 41 per cent.[266]

The generally conceded influence of sex on this correlation is significant.[270] Excluding patients with a diastolic presure under 90, the incidence of prior hypertension was 29.7 per cent in males and 49.4 per cent in females in one series,[156] by the new criteria for high blood pressure proposed by Master and associates,[144] the figures were 27.2 and 71 per cent, respectively. Other figures to be found in the literature are: 37.2 and 63 per cent, respectively,[34] 48 and 69 per cent,[22] 36.8 and 67.2 per cent,[213] 38 and 64 per cent,[248] 39.2 and 65 per cent,[71] and 48.9 and 79.4 per cent.[209] Obviously, coronary disease is even more likely to affect women with hypertension than men.

Antecedent hypertension is found the oftener, the older the patient. Among young patients with coronary disease, the incidence of hypertension was only little higher than normal.[156, 263]

Experimental hypertension also seems to have a detrimental effect. Cholesterol- and propylthiouracil-induced atherosclerosis in dogs was intensified by hypertension produced by injecting silica into the renal arteries.[163, 164]

There is no reason to believe that persons with hypertension undergo different coronary arterial changes than persons with normal blood pressure. The changes in the coronary arterioles in malignant hypertension were found to be most inconsistent:[109] (*1*) there was marked variation in different arterioles in the same case and in different segments of any one arteriole, (*2*) the early changes, which consisted of an increase in the medial nuclei and hyperplasia of the internal elastic lamella, do not progress at the same rate or to the same degree as similar arteriolar changes elsewhere. Occasionally, the coronary vascular tree is unaffected despite widespread vascular disease.[163] There is some evidence that the serum beta-globulins are increased in both clinical and experimental hypertension.[414] A possible genetic relationship between the two conditions is discussed by Thomas,[231] who says: "it is likely that the same heritage is expressed more often as hypertension in females and as coronary artery disease in males." Possibly, the relatively higher incidence of infarction among persons with hypertension may be due to the greater oxygen needs of the left ventricle when maintaining higher pressures and the greater severity of the atheromatous process.[52] According to Wilens and Elster,[257] hypertension provides "a positive filtration pressure against a permeable endothelial surface, thus enabling lipid-containing substances to enter the intima. . . . There is probably a threshold value of filtration pressure below which fluid entering the intima is largely devoid of lipid."

On the other hand, some do not believe that hypertension is an important etiologic factor in coronary disease. Thus, Sigler[207] calls attention to the fact that the blood pressure in young (under the age of 40) patients with coronary disease is normal; in patients over the age of 40, the incidence of raised blood pressure is no higher than might be expected in an aging population. When higher blood pressure levels than are usually con-

sidered normal were used as normal values, Master and co-workers[141] found a relationship between hypertension and coronary occlusion only in men over the age of 65, and in women

DIABETES MELLITUS There is a definite causal relation between diabetes and heart disease Coronary atheroma develops much more frequently in diabetics than in the general population, and coronary disease appears at an earlier age and in severer form Diabetics with coronary disease die at a younger age than nondiabetics, it was found in one study.[60]

The first to note the presence of diabetes and angina pectoris in the same patient was Seegan,[206] in 1864; 20 years later Vergely[239] suggested the possibility of a relationship and proposed that the urine of all patients with angina pectoris be examined for sugar.

The likelihood of death due to myocardial infarction is more than twice as great for the diabetic as for the nondiabetic. In one series, the incidence of death from coronary occlusion was 10 8 per cent for the diabetic and 4.2 per cent for the nondiabetic.[192] Coronary occlusion or myocardial infarction was found in 43.8 per cent of diabetics and in 20.1 per cent of controls in a postmortem study.[60] Other reports, although varying greatly in criteria and type of material, nevertheless point to a comparable preponderance of heart disease in diabetes. The percentage of patients with clinical diabetes in whom coronary occlusion occurs is variously given as 7.9 per cent,[54] 8 per cent,[212] 11.2 per cent,[143] 14 per cent,[133] and 17 5 per cent.[97] About 1 in 10 patients with coronary disease treated in an outpatient clinic had diabetes.[120]

Women with diabetes are even more vulnerable to coronary disease than men or than nondiabetic women; they are fourteen times as apt to have coronary occlusion as women without diabetes. On the basis of published figures, it has been estimated that 30 9 per cent of the women and 8 3 per cent of the men with severe coronary disease are diabetics [54]

The likelihood of arteriosclerotic heart disease developing in a diabetic is a function of the patient's age and the duration, rather than the severity of the diabetes [129, 218] On the other hand, some have claimed that if the disturbed carbohydrate metabolism is well controlled, onset of atheroma may be delayed.[230, 260] The presence of hypertension increases the likelihood of coronary disease in diabetics.[218]

Not everyone subscribes to the theory of a close relation between diabetes and coronary disease. One study of material from the Mayo Clinic concluded that the incidence of all grades of coronary disease is no greater in diabetics than in nondiabetics, when coronary disease occurs in the diabetic, however, it is apt to be severe.[253] Another report states that diabetes has no significant effect on the mortality rate in coronary disease.[213] Diabetes had no effect in inducing arteriosclerosis of the aorta, although this is a somewhat different problem [63]

Why the diabetic is particularly vulnerable to coronary disease is a question still largely unanswered Hypertension, which is not especially frequent in diabetes, is probably of small importance. In this connection, it is interesting that atheroma in the pulmonary artery and its branches is not rare in the diabetic, hypertension in these cases, in the absence of increased pressure in the lesser circuit, can play only a small role.

With the exception of rheumatic or syphilitic infection, the etiologic role of infection in arteriosclerosis is generally held to be minor, if any While infection, with its resultant toxemia and opportunity to damage vessel walls, is extremely frequent in diabetes,[244] and arteritis is often seen, particularly with neighboring infection of soft parts, this is not a factor in the production of atheroma

There is little evidence that the disturbed metabolism of carbohydrates and proteins in diabetes bears any relation to coronary disease Severe coronary disease has undoubtedly developed in many diabetics whose blood sugar has been kept within normal limits by insulin In explanation it has been suggested that fluctuating blood sugar concentrations or acidosis may cause intermittent swelling and thereby a weakening of the intercellular substance of the intima The effect of acidosis on the arteries is not known; while reversible T wave changes have been described in diabetic shock,[151, 221] these are without doubt the result of electrolyte disturbances rather than of cardiac ischemia Unexplained acidosis in

diabetes should lead the clinician to search for an unrecognized cardiac infarct.

In alloxan-diabetic rabbits, little or no atherosclerosis develops, despite a rise in blood cholesterol level. Healthy rabbits, on the other hand, become arteriosclerotic when fed cholesterol, but when such rabbits are rendered alloxan-diabetic, the arterial deposits of lipid do not regress.[57]

One theory of the diabetic's increased susceptibility to atherosclerosis is based on the disturbed lipid metabolism in diabetes. Hyperlipemia, in some cases severe, is usual in diabetes, especially when it is poorly controlled, but no correlation has yet been established between the blood lipid level and the incidence or severity of the coronary disease in diabetics.[11, 129, 218] An abnormally high concentration of chylomicrons has been reported,[271] and the Sf 35-100 class of lipoproteins appears to be increased in diabetics with peripheral vascular disease.[40, 90]

It is noteworthy that the glycogen content of the heart is increased in diabetes. The special tendency for glycogen deposits about the margins of infarcted or fibrotic areas may mean that these muscle fibers are unable to utilize glycogen as fully as healthy muscle. Since glucose is essential for heart muscle, *it has been suggested that excessive glycogen* storage by the heart may represent an effort to tide the heart over any period of deficit in usable carbohydrate. Apparently, the heart is not harmed by the presence of the extra glycogen, but in other respects cardiac metabolism is considerably deranged in diabetes.[254]

OTHER METABOLIC DISORDERS

The etiologic relation of hypoglycemia and hypocalcemia[123] to coronary disease has been suggested, but the evidence is skimpy and both factors may be disregarded until further proof is available.

Porphyria in association with infarction has been described in 1 case.[2]

Disturbances of uric acid metabolism have been linked with coronary disease. Gout and arteriosclerosis are both diseases which affect males predominantly, and occasionally are found in the same patient. I have seen 3 cases in which the first attack of gout followed close on the heels of an infarction, and 3 cases are reported in the literature.[9] In a thorough investigation of uric acid metabolism in diabetic patients with coronary disease, the average value of the serum uric acid was found to be 5.13 (+0.12) mg. per 100 cc. in the group with coronary disease, 4.85 (±0.07) in matched controls, and 4.64 (±0.6) in unmatched controls.[88] Levels above 6 mg. per 100 cc. were found in 22 per cent of the coronary group and in only 6 per cent of the unmatched control group. The investigators felt that the blood levels of uric acid and lipids were closely related, but that another constant was even more important than the level of serum uric acid alone:

$$K = \text{serum uric acid (mg./100 cc.)} \times \frac{\text{total serum cholesterol (mg./100 cc.)}}{\text{serum lipid P (mg./100 cc.)}}$$

The suggestion is made that uric acid may be an intimal conditioning agent (surface-active agent) which furthers cholesterol deposition, especially if the serum lipids are unstable.

GALLBLADDER AND BILIARY TRACT

It is widely believed that there is a close relation between the coronary arteries and the gallbladder. Thus, it is often assumed that patients with gallbladder disease are more susceptible to coronary disease, and that reflexes *from the gallbladder and biliary tract* initiate changes in the cardiac circulation which adversely influence the heart and make a definite diagnosis difficult.

In one series, 9 per cent of the men and 7 per cent of the women had gallbladder disease; these figures seemed to be well in excess of the probable incidence of 5 to 6 per cent in the general population.[199] In contrast, another study reports an incidence of 13 per cent among patients with coronary disease and of 22 per cent in a control group of the same age, race, and sex.[22] Data based on postmortem material do not support the theory of a relationship between the two conditions.[223, 242] It has been suggested that infection from the gallbladder may increase the likelihood of coronary disease,[117] but the merely fortuitous and occasional coincidence of the two common ailments of middle age seems much more likely. *Were careful statistical analysis to es*tablish the existence of a relationship, it would probably be found in the fact that both

conditions may be related to disorders of lipid metabolism

Decrease in coronary flow after biliary tract stimulation has been reported[44, 57, 112] and denied[227, 261] In animals, increasing the intrabiliary tension by a small balloon in the gallbladder gave varying results, the effect, if any, was always in the same direction as on the blood pressure and was abolished by prior use of atropine.[59] Observations on man are somewhat more convincing, but give no real clue as to why cardiac changes occur. Distention of the common bile duct at operation or pressure on the gallbladder may induce anginal pain.[169] Electrocardiographic abnormalities, especially flattening or inversion of T waves, and anginal pain have been reported in acute gallbladder disease, after cholecystectomy, the pain disappeared and the electrocardiogram reverted to normal[24, 72]

Whatever the effect of biliary tract reflexes on the heart may be, it is undeniably true that a differential diagnosis is difficult at times In general, it may be safely assumed that a patient with angina of effort has coronary disease, whatever the state of his biliary tract It is also safe to assume that a patient with gallstones or a gallbladder which cannot be visualized by careful and repeated roentgenography has chronic cholecystitis When the signs and symptoms point both to coronary disease and to gallbladder disease, the clinical assumption should be made that the patient is suffering from both conditions, until the contrary is proved. In some cases, the diagnosis may not be clear until after cholecystectomy, if then, but in no case should a patient be subjected to an operative procedure in the absence of clear-cut roentgenographic or physical evidence of gallbladder disease No patient of mine undergoes surgery if there is no definite roentgenographic indication, on the other hand, precordial pain even of the classic anginal variety, is in rare cases somewhat improved after removal of the gallbladder In most instances, cholecystectomy has no effect on the concomitant coronary disease, if present. In any case, the operative risk of gallbladder surgery in well-prepared patients with coronary disease is little, if any, greater than in patients with normal hearts[205, 159]

GASTROINTESTINAL TRACT Statistical evidence that coronary disease is more common among patients with peptic ulcer, as some have claimed, is scant[45, 102, 191, 199] Postmortem data seems to indicate that the association is fortuitous[242] This is my opinion, too[151] The high-fat diets usually prescribed in the treatment of ulcer may accelerate the course of an already established coronary atheroma.[140] It has been suggested that peptic ulcer, by stimulating the vagus nerve excessively and for a long time, may reflexly affect the coronary arteries[161]

Other diseases of the gastrointestinal tract seem to have little relation to coronary disease One report states that 17 per cent of patients with coronary disorders had diverticuli, as compared to 5 percent of controls.[22]

VACCINIA Eight cases of infarction have been reported in men over 50 in the second week after vaccination for smallpox. This, if confirmed, will be a matter of clinical importance[145a]

SEASONAL FACTOR IN MYOCARDIAL INFARCTION

At least in the northeastern United States the time of year seems to affect the incidence of infarction slightly In one series, 30 per cent of attacks took place in the winter months (December through February), and only 20 per cent in June through August.[16] Other reports contain similar figures,[16, 72] 61 per cent of patients in one series suffered attacks in the autumn and winter[56] Even in the mild climate of Los Angeles, a similar seasonal incidence was found, this was ascribed to the greater number of infections in the colder months[113]

Other investigators, however, have not found any appreciable seasonal variation,[115, 142, 156] one report, for example, notes only a slight increase in November, and a somewhat greater mortality in March and November[253]

The stress of extreme heat or cold would seem to be detrimental In Texas[111] and in Alabama[137] the greatest number of attacks occur in July and August, the period of greatest heat Similar observations have been reported for Egypt,[113a] but another Texas physician noted more attacks during the winter months[204a] Of the last 500 cases of infarction which I have observed, 55 per cent occurred

between November and April. In my experience, the number of cases rises rather abruptly after a heavy snowfall, often in automobile drivers who attempt to push a car out of a snow drift.

Cold weather usually makes anginal pain worse and considerably reduces exercise tolerance; the reverse is true of pleasant, warm weather. Patients who feel better in the summer, it has been reported, react favorably to vasodilator drugs, the prognosis is not as good in patients who do not respond to these drugs or to warm weather.[74]

EMOTIONAL AND PSYCHOGENIC FACTORS

Psychogenic factors and the emotions may play a role in the pathogenesis of coronary sclerosis, in the production of cardiac pain, and in the precipitation of myocardial infarction

ROLE IN PATHOGENESIS OF CORONARY SCLEROSIS The stresses and strains of life today which were absent in former days are commonly advanced as an explanation for the possibly increasing prevalence of coronary disease. To my mind, this is a singularly unconvincing theory The fears, anxieties, and emotional strains under which our forbears lived were undoubtedly as great as ours, and there is every reason to suppose that life was just as nerve-wracking then as it is now Not so long ago, men were thought to be more vulnerable than women to arterial disorders because their lives had more anxieties and strains This is no longer current belief, in coronary disease, too, we will have to look elsewhere for an explanation of its increase.

The thesis that persons with coronary disease exhibit a special type of personality pattern has been accepted by many cardiologists for a decade or more The theory has been propagated most actively by Dunbar,[58] Arlow,[8] and the Menningers.[147] A summary of the views of several investigators of the behavior patterns and personality factors in persons with coronary artery disease, as given by Gildea and cited by Miles and associates[151] includes: *"Great need for and respect for authority. Unremitting workers Stick to one occupation. Compulsive. Low awareness of body symptoms Feelings of insecurity and inferiority. Compensatory workers (the job serving as a defense against anxiety). Sociable and well liked."*

Dunbar's detailed study by psychiatric interviews of hospitalized patients with coronary occlusion, and her inferences, have apparently furnished the basis for most of the opinions found in the literature. Both Dunbar and Arlow concluded that a clear-cut constellation of personality traits can be detected in individuals with coronary artery disease. The patients in the series studied showed a high record of previous illness, a high marriage rate, and had large families, there was a decided trend toward completion of whatever scholastic unit was undertaken, as well as a tendency to stick to one job for many years, to work long hours "under considerable stress and strain," and not to take vacations. There was little interest in sports or hobbies, but marked interest in philosophy and intellectual pursuits They exhibited considerable evidence of control, "presenting a surface calm with little of the appearance of strain that is evident in patients with hypertensive cardiovascular disease"

Relatively few neurotic traits were found, but as children these patients tended to be stubborn and self-willed, and were apt to brood, constipation during childhood was common. The psychodynamic importance of their childhood conflicts with authority was emphasized by the investigators There was an early competitive relationship with a much feared and envied parent (usually the father); the characteristic defense mechanisms for dealing with this focal conflict were repression and identification. These mechanisms served the purpose only inadequately, for the patient continued to re-experience his old conflict with authority repeatedly as he unconsciously recreated the original competitive situation in new forms The compulsive drive to success by means of hard work and self-discipline brought no gratification or relief from tension

The "apparent strength and extreme brittleness of the defenses" was noted, as well as that their only strength was in the fact that their "highly unified and rigidly crystallized life role is culturally well adapted and very rewarding" When this "life role," which had served as a major defense against inner poverty or insecurity, was threatened or injured

by outward circumstances, the patient became psychologically self-destructive and fell prey to somatic accidents, such as coronary occlusion.

Because of the faulty identification with the father, the patient suffers from a deep-seated lack of conviction about himself; this accounts both for the compulsive competitiveness and for the traumatic effect of failure, when it occurs. Being inwardly convinced that he is a sham, the patient cannot accept success. In Arlow's opinion, "The coronary patient thus evades a neurosis by means of a character deformation. He pays the price, however, in a pre-disposition to this somatic disease. Together with constitutional and other factors this longstanding unabated tension helps consolidate the predisposition to the development of this illness." And Dunbar concluded, "This personality constellation plays an important role in bringing about the coronary accident and has a bearing on prognosis and therapeutic management."

On the basis of a careful, detailed study of 46 patients with coronary disease and of 49 controls, Miles and co-workers[144, 160] were unable to confirm Dunbar's and Arlow's conclusions. They note that some of the discrepancies might lie in the different sociocultural composition of the two groups of patients. Dunbar's group of 22 patients was 59 per cent Jewish; their 46 patients were 35 per cent Jewish. They found that the incidence of "coronary personality" was more than twice as great in the Jewish group, all but one of whom had fathers who had emigrated from central or eastern Europe, in many cases there had been a good deal of emphasis on education, material success, and a rise in social scale. In Dunbar's study no allowance had been made for these factors, so that her postulated relation between personality and coronary disease might in fact not be as close as she thought.

Comparison of specific personality traits in the patients with coronary disease and in the controls revealed only very slight differences. A slighter tendency to introspection and greater difficulty in handling aggressive tendencies was noted in the coronary group as compared to the control group, but on the whole the similarities between the two groups were more striking than the differences. "The coronary patients had tended to work harder, under more stress and strain. . . . Only a few more of the coronary patients than controls showed a consistent tendency toward compulsive striving, ascetic self-discipline, and great need to 'get to the top' in their chosen work."

Their data suggested that "the major factors in the genesis of atherosclerosis included maleness, body build, and some intrinsic metabolic fault, probably inherited."

Miles and associates thought that so far as the general adjustment after the coronary attack was concerned, the correlation between the patient's character structure and his adaptation to life seemed to be close. Patients in whom the illness caused the collapse of their self-image as strong and successful men usually suffered from severe and prolonged anxiety, depression, and neurotic symptoms after the attack. The convalescence of the majority, however, was not marked by severe neurotic reactions.

The mechanisms by which psychic and emotional impulses are translated into organic changes are still largely unknown, it seems only barely possible that they may occur. It is known that fear can produce electrocardiographic changes.[20, 135] Bombardment of the coronary vessels by nerve impulses which may affect the vessels' tone, the release of epinephrine and other endocrine secretions which influence the coronary circulation, changes in the body's internal environment by way of altered metabolism of lipids or other substances, singly or in combination, conceivably might affect the vessel walls eventually. But whether they actually do is still largely conjectural, there is no real evidence that such factors are important in the genesis of atherosclerosis.

ROLE IN CARDIAC PAIN Emotional strain, especially if unpleasant, often produces anginal pain in patients with angina pectoris, which is an organic disease since it is almost always a manifestation of coronary atheroma. Once considered a neurosis pure and simple, the emotion-induced anginal pain is a true cardiac neurosis. Emotional tension can increase the heart rate, elevate the blood pressure, and raise the cardiac output.[220]

A study[262] of two groups of patients with cardiac disease, one with heart pain and the

other with cardiac insufficiency but without pain, revealed that four fifths of the first group and only one fifth of the second had some psychologic disorder before the onset of cardiac symptoms In many patients, the pain seemed to be a late manifestation of a chronic anxiety state and had often been precipitated by a disturbing emotional event. This was found not only in patients with functional pain but in true angina pectoris as well The attention of a patient with an organic lesion may be focused on the diseased organ, and the shunting of the emotional stream to the site of least resistance thus made easier This is an important factor in causing a state of invalidism in a patient with myocardial infarction and marked anxiety, the pain pathway, once established, grows increasingly easy to use

Cardiac mimicry is a special form of cardiac neurosis. Patients with functional pain will often, if questioned closely enough, acknowledge knowing someone with closely similar cardiac symptoms—a friend, a relative, or even someone of whose symptoms they have read However, one must guard against a mistaken diagnosis of mimicry The wife of one of my patients with myocardial infarction insisted that she had symptoms closely resembling those of her husband In view of her anxiety and the long, trying period through which she had just passed, cardiac mimicry seemed a possibility The electrocardiogram, however, showed the changes of a recent infarction.

IATROGENIC FACTORS[55] Careless, or even prudent, remarks by the attending physician or by well-meaning friends may intensify the distress of the patient with true angina pectoris. The utmost care must be exercised not to reinforce the patient's anxiety and to avoid the induction of an unwarranted invalidism (*see* Chapter 11 for illustrative case histories)

PRECIPITATION OF INFARCTION Although most patients with coronary disease withstand emotional bouts without much harm, coronary insufficiency, as manifested by anginal pain, may be induced by excessive emotion. Such a state, if prolonged, probably leads to some degree of structural cardiac damage But the problem to be considered here is whether emotional shock can cause a major infarction, as some believe.[25, 109] The fact that an infarction has been known to follow an emotional upset is no proof of a causal relationship. Nevertheless, in a few cases I have had little doubt that an emotional shock actually caused a myocardial infarction. There is no incontrovertible proof nor is the mechanism entirely clear, but I must conclude that such cases, although rare, do occur.

It is somewhat less doubtful that sudden death can occur from a severe emotional trauma Death from a "broken heart" is more common in fiction, but it may occur in real life—John Hunter and Philip V are examples Boas[25] suggested as possible mechanisms the outpouring of epinephrine, which may induce ventricular fibrillation (especially in the presence of coronary disease), or possible vasomotor changes which might induce anoxia and fibrillation

Another precipitating factor is the shortened clotting time and the increased viscosity of the blood which emotional stresses (anxiety, fear, anger, hostility) may induce[78, 203, 204] It has been reported that they also promote hypercholesterolemia[109]

ACUTE HYPOTENSION AND OPERATIVE PROCEDURES

Since the head pressure in the coronary arteries is identical with that in the root of the aorta, aortic hypotension will result in a fall in the coronary pressure In the presence of a reduced coronary flow, any further reduction may cause muscle necrosis

Sustained shock or hypotension may cause a major myocardial infarction in a patient with coronary disease. Even when the arteries are normal, shock may end in subendocardial infarction I have seen fatal infarction in persons with coronary disease follow accidents with crushing injuries as well as from prolonged hemorrhagic shock due to gastrointestinal bleeding. Prolonged hypotension due to bleeding from a peptic ulcer is particularly dangerous in the older age groups or in those with a history of coronary disease. The old practice of depending on the fall in blood pressure to stop the hemorrhage is particularly pernicious in such cases; early transfusion is the proper treatment.

The sudden drop in blood pressure in-

duced by drugs when testing for the presence of a pheochromocytoma may cause acute coronary insufficiency. In a case recently reported, a drop in blood pressure from 160/90 to 95/40 was followed by severe substernal pain and T wave inversion [167]

Now that patients in the older age groups and those formerly considered poor risks are safe candidates for surgery, postoperative infarction is becoming more common The risk of cardiac damage is great if the blood pressure is permitted to fall, especially when spinal, local, or pentothal[41] anesthesia is used. Any form of anesthesia in which the patient is awake has the further hazard of the patient's apprehension and fear. Adequate sedation should therefore be administered and the blood pressure kept at safe levels when spinal anesthesia is used

With general anesthesia, oxygen should be used liberally to guard against anoxia. Muscle-relaxant anesthetic drugs, which diminish the movement of the diaphragm and the accessory respiratory muscles with resultant decrease in the venous return to the heart, may also cause anoxia.[17, 246]

Wasserman and co-workers[246] have reviewed the literature on acute hypotension and postoperative infarction and have added 25 cases of their own In addition to the reduction in coronary blood flow which may result from operative hypotension, they found stasis and narrowing of blood vessels due to circulating epinephrine, increase in the number of platelets, and a decrease in the antithromboplastic activity of the plasma. In the postoperative period, an increase in blood platelets and circulating fibrinogen are contributory factors.

PHYSICAL STRAIN AND TRAUMA

Most cases of myocardial infarction have no definite history of a precipitating factor or event People tend to ascribe any misfortune to some antecedent occurrence, but the skillful physician can usually sift this out without great difficulty On the whole, there is little reason to incriminate unusual physical exertion, overindulgence in food, in sports, or in travel, sexual excesses, emotional upsets, or bad dreams, however, all of these may precipitate anginal attacks The timid patient who resolutely avoids all exertion or emotion can be assured that myocardial infarction cannot be avoided by a completely vegetative existence.

In one carefully studied series,[1-6] precipitating causes could be established only in 9.5 per cent, they consisted of severe emotional upsets, upper respiratory tract infections, operative procedures, severe exertion, insulin overdosage, and disturbing dream. Other reports give unusual exertion preceding the attack in 2[143] and in 2 5 per cent.[196] Still others report much higher figures, in one series,[22] vigorous activity preceded the attack in 22 per cent; in another,[84] it may have been "a factor in the development of infarction" in 21 per cent Judging from studies on young adult patients, strenuous activity probably precipitates acute attacks more often in the younger than in the older patient [209] In one series of patients, all under the age of 40, the attack occurred relatively more often after exertion than during mild activity or sleep,[209] the victims had been in the Army only for a short time, which may indicate that the rigors of Army life played a precipitating part In another series, 3 young soldiers died at stool, bearing down at stool (the Valsalva maneuver) is "notoriously dangerous for cardiac patients "[75]

Further discussion of the relation of physical strain and trauma to acute infarction will be found in the chapter on medicolegal aspects of coronary disease.

OTHER POSSIBLE PRECIPITATING FACTORS

Many conditions closely related in time with the onset of myocardial infarction have been described While they cannot be accepted as being causally related to the infarction, they are being listed here merely as conditions which preceded infarction

Gelatin nephrosis,[210] intravenous saline injections,[29] Friedreich's ataxia,[168] diphtheria,[17] and temporal arteritis[39] have all been reported in association with infarction or "coronary occlusion " Polycythemia has been both incriminated as a cause of coronary thrombosis even without atheromatosis,[175] and freed from blame [174] I have seen several cases of myocardial infarction in association with polycythemia vera A distinct thrombotic tendency is characteristic of polycythemia. Coal-gas poisoning is followed by cardiac sequelae

in less than 1 per cent of cases; a single, rather inconclusive case of infarction has been described[106]

Experimental chemical poisoning—for example, allylamine poisoning in dogs[247]—can damage the coronary arteries The lesions, however, are not comparable to atheroma in man, although it is just possible that a similar effect might occur in man

There is no evidence that excessive adhesiveness of blood platelets has any relation to infarction in man[61]

Occlusive disease of peripheral arteries and coronary sclerosis are often seen in the same patient,[89] this is scarcely surprising, since both are conditions which affect the middle aged and the old, especially persons with diabetes.

CORONARY ARTERY LESIONS OTHER THAN ATHEROMA

Atheroma accounts for 90 to 95 per cent of the lesions of the coronary arteries The list of conditions which may affect the coronary arteries in the remaining 5 per cent of cases is long

- Aneurysms
- Embolic and thrombotic diseases
- Neoplastic disease
- Trauma
- Congenital anomalies
- Medial calcification of infancy
- *Inflammatory lesions syphilis; tuberculosis,* other bacterial infections, rheumatic fever, *polyarteritis nodosa; thromboangiitis obliterans*

MEDIAL CALCIFICATION OF INFANCY

This lesion is apparently a distinct pathologic entity. It has been given many names. medial coronary sclerosis,[81] and medial calcification with fibroblastic proliferation of the intima[223] being two of the best. The most recent review[211] *of the subject lists 33 cases from the* literature[67, 78 143] (19 boys, 12 girls, 2 sex unknown), and a few cases have been added since.[195] All cases have occurred in children up to and including the age of 27 months.

The essential lesion is found in the larger coronary arteries. It consists of a fibroblastic proliferation of the intima and calcification which starts close to the lamina elastica interna and spreads *to the media and to the proliferated* intima; eventually, the media becomes extensively involved. Obstruction of *the lumens, recanalization, and infiltration of* the vessel walls by various cells—round, giant, and eosinophilic—*may all be found in varying* degrees. Myocardial infarction and calcification may be present if the vessel is occluded. The left ventricle and papillary muscles are frequently involved. The course after onset is short (days or weeks), and steadily downhill

The cause of the lesion is unknown Stryker,[222] in his review, notes that severe renal lesions were found in some cases. He goes on to say:

> . . . in these cases the arterial lesions may represent metastatic calcification secondary to an altered calcium-phosphorus ratio in the blood *Similar lesions are sometimes found in "renal* rickets" (renal osteodystrophy) Altered calcium-phosphorus ratios likewise occur *in primary para*thyroid hyperplasia and in primary or destructive osseous disease, and thus these conditions also may be etiologic factors Calcification of arteries has occasionally been observed following an in*take of excessive amounts of vitamin D Other* [illegible]
>
> medial calcification, and thus no one of them can be accepted as the sole cause. The most attractive hypothesis is that in all cases an embryonally *weak protoplasm is present in these infants,* and on this poor ground substance any one of many factors may act as a precipitating mechanism Such a factor has been postulated . . as a factor in arteriosclerosis of the adult type and may be *equally a factor in the infantile type*

CORONARY NECROSIS OF NEWBORN

In 1949, Gruenwald[103] reported 21 cases of this condition. He found these lesions in 9.5 per cent of cases of infants who died before the age of 3 days which came to autopsy Usually, the lesion was found in infants who had suffered some asphyxia. Occasionally, *similar changes were seen in the liver arteri*oles. The outer part of the media was consistently affected, the inner media and the intima being spared No healing stages were found Whether this condition is in any way related to the medial calcification of infants is conjectural.

INFLAMMATORY LESIONS There is little doubt that the coronary arteries, especi-

ally the myocardial branches, may become involved in the course of any infectious disease. The literature on the subject is not prolific.[253, 254] Evidence in favor of infection as a cause of sclerosis includes the fact that there is a direct anatomic pathway between the paralaryngeal lymph nodes which drain the coronary sinuses and the systemic circulation.[117] On the other hand, other investigators have found little evidence that infection plays a role in the genesis of atheroma

Arteritis may arise by extension from neighboring tissues, or have a mycotic origin. Secondary thromboses may occur. Primary arteritis of the coronary vessels has also been described.

Obliterative endarteritis has been noted by some. Possibly, such cases were the end result of acute inflammatory processes The coronary arteries are fairly often affected in subacute bacterial endocarditis, and areas of myocardial infarction are often found in this disease.

The occasional occurrence of coronary thrombosis due to "infectious coronaritis" resulting from coronary localization of a more or less generalized arteritic process has been reported.[233]

Syphilis Syphilitic narrowing of the coronary arteries is not uncommon in syphilitic aortitis It occurs in about 20 per cent of such cases,[264] although higher figures have also been reported. Myocardial infarction secondary to stenosis, however, is rare, occurring in only 7 5 per cent of cases with stenosis The infrequent occurrence of infarction may be due to the slow course of syphilitic disease, which allows time for a collateral circulation to develop. Of 326 cases of myocardial infarction in one report, only 3 were secondary to syphilis; the age of the patients with luetic coronary narrowing ranged from 20 to 70 years In 72.5 per cent of the cases, both coronary arteries were involved, when only one artery was involved, it was more commonly the right. In most cases there is an associated aortic insufficiency, and in some cases there may be aortic mural thrombi and, rarely, coronary embolism Acute myocardial infarction has been reported in a 26-year-old woman with presumed syphilitic aortitis and coronary ostial stenosis[219] Myocardial infarction has also been reported in association with gumma of a coronary artery and occlusion[121]

Syphilitic aortitis is productive and obliterative, involving all three coats of the vessel wall. The process usually begins with an accumulation of small round cells around the vasa vasorum in the adventitia. The inflammation extends along smaller vessels and involves the media and intima In the media, the muscular and elastic tissues are replaced by infiltrations of lymphocytes and small round cells; the intima is thickened by vascular inflammatory plaques These edematous lesions may involve the entire root of the aorta (girdle of Venus), including the ostia of the coronary arteries where they penetrate the wall of the aorta Involvement of the proximal portions of the coronary arteries is said to be frequent because a branch of the coronary artery supplies the first portion of the aorta, where aortitis is most common. Syphilitic lesions of the coronary arteries distal to their orifices are uncommon

Syphilitic and arteriosclerotic involvement of the same coronary artery often occurs The syphilitic lesion may be distinguished by the longitudinal wrinkling of the intima, the edematous plaques around the ostia, the thickening of all the vessel walls, the patency of the terminal artery, and the perivascular round cell infiltration The arteriosclerotic lesion is characterized by the absence of edematous plaques and of intimal wrinkling, by the presence of yellow plaques throughout the length of the artery, and by the hardness and brittleness of the vessel.

Syphilitic involvement of the ostia is more apt to occur if the origins of the coronary vessels are abnormally high in the aorta The process seldom dips down into the sinuses of Valsalva

Tuberculosis This is an insignificant cause of coronary occlusion, and rarely involves the coronary arteries. If it does, miliary tuberculosis, or mediastinal or pericardial infection is usually the cause.

Brucellosis Coronary involvement was reported in 26 per cent of a series of cases of brucellosis[159]

Salmonellosis Coronary arteritis has been reported in a case of sepsis due to infection with *Salmonella choleraesuis*, var Kunzendorf[12] There was thromboarteritis of the left anterior descending coronary artery about 2 cm from the aortic orifice, and infarction of the involved myocardium.

Malaria The coronary arteries have been reported to be involved in malaria[149]

Rheumatic Fever The subject of coronary artery involvement in rheumatic fever was reviewed by Karsner and Bayless,[118] and by Gross and co-workers[102] In the largest series reported since then coronary involvement was found in all of 18 cases of rheumatic fever that came to autopsy,[185] and several other reports give some cases[21, 53, 187] The clinical importance of rheumatic coronary artery disease is rather difficult to evaluate Some investigators believe the changes are rarely of clinical significance, as compared to the myocardial lesions[112, 222] Others think the lesions important[102, 118] Clinically significant occlusion of a main coronary artery is rare in acute rheumatic fever, in 1 case, there was coronary occlusion with extensive infarction, and in another thrombosis of the left circumflex artery including the main trunk[102]

Opinion on the relation between rheumatic fever in childhood and subsequent atheromatous heart disease is divided Some hold that there is no evidence to suggest such a relationship[78] In one report, only 2 7 per cent of cases of infarction that came to autopsy had a definite history or the lesions of previous rheumatic fever[135] Some examples of the association of rheumatic fever and coronary lesions are known It has been suggested that lesions in the main coronary arteries and in their branches may account for some of the symptoms of angina pectoris in chronic rheumatic valvular disease

In 3 cases of sudden death in rheumatic fever, distinctive lesions were found at the base of the aorta, with histologic evidence of widespread vascular disease in 2 of them.[89] In all 3 cases, the coronary arteries showed extreme fibrosis, cellular accumulation, and "collagenous" masses in the walls of the arteries It was concluded that "the cause of abrupt death in each was an acute anaphylactic coronary angiitis superimposed upon a low-grade rheumatic carditis."

"Atypical" coronary disease has been reported which it was thought might have been "rheumatic."[249]

Polyarteritis Nodosa The coronary arteries are involved in 70 per cent of the cases. With the exception of the renal arteries, the coronaries are the most often affected by this disease

A number of reports have described this complication of polyarteritis nodosa.[99, 110, 209] In one series of 23 cases, the coronary arteries were involved in 17.[99] Myocardial infarction has been reported in 1 case[176]

Thromboangiitis Obliterans Perla[179] was the first to report involvement of the coronary arteries in this disease. Since then a number of cases have been reported.[5, 34, 65, 90, 176, 200] In one series of 50 cases, 5 showed involvement of the coronary arteries,[200] in another series of 40 cases gathered from the literature in which autopsy reports were available, coronary occlusion was the cause of death in 10,[65] in a series of 225 unselected cases, there were only 7 with coronary artery involvement;[5] 1 case of the disease and coronary occlusion with recovery has been reported,[30] and 1 case with myocardial infarction[176]

CORONARY ANEURYSMS Except for the aneurysmal dilatations of polyarteritis nodosa, aneurysm of the coronary arteries is rare Localized coronary artery aneurysm has been reported in 51 cases congenital, 15; mycotic-embolic, 12, arteriosclerotic, 6, syphilitic, 6, purely mycotic, 1, rheumatic, 1, and unclassified, 1.[228] A double arteriosclerotic aneurysm of the left coronary artery brings the total number to at least 52[18] The clinical diagnosis has been made only once; a bulge was noted in the auriculoventricular niche, with pulsations not synchronizing with those of the ventricle[48, 172]

Arteriosclerotic Aneurysm This type is found most commonly in persons past middle age The age range in 17 cases was 32 to 77 years, only 1 of the 17 was a woman, the left coronary artery was involved in 13, the right, in 4, multiple lesions were found in 3;

and in 1 both the right and left coronary arteries were involved[177] Extensive atheromatosis of the coronary artery was present in all cases, and the aneurysmal sac in many was filled with thrombotic material, this probably helped to prevent rupture. Of the 14 deaths that could be attributed to cardiac causes, only 5 were directly caused by the aneurysm in 3 rupture of the aneurysm into the pericardial sac, causing cardiac tamponade, in 1 rupture into the myocardium of the right ventricle, in 1 rupture into the wall of the pulmonary artery In the remaining 9 cases, coronary occlusion or cardiac failure was the cause of death In a case recently reported, that of a 69-year-old woman, angina pectoris, and finally cardiac death, was presumably due to a large (5 cm) aneurysm compressing the left coronary artery, the coronary arterial tree showed only minimal changes otherwise[223]

Multiple aneurysms of the right coronary artery have been reported twice.[187, 198]

Dissecting aneurysm The coronary vessels may be involved in dissection either as a result of intimal rupture of an arteriosclerotic or aneurysmal coronary artery or by extension of a dissecting aneurysm of the aorta In 1 such case reported, the dissection continued into the wall of a coronary artery, resulting in coronary occlusion and myocardial infarction[240] In several cases, an aortic aneurysm dissected back to the annulus of the aortic valves and involved the coronary orifices The subject has been reviewed by Oram and Holt[171]

Congenital Aneurysm This condition is discussed later in the chapter

Syphilitic Aneurysm Only 7 cases have been reported[49]

Mycotic Aneurysm This aneurysm is of embolic origin, and is most often encountered in bacterial endocarditis.[33]

CORONARY EMBOLISM In comparison to thrombosis, embolism of the coronary arteries is exceedingly rare. Reviews appeared in 1932,[201] in 1940,[194] and in 1953[33] Diagnosis was made during life in 1 case.[83]

The embolus may consist of bacterial vegetations from the heart valves, fragments of vascular thrombi, tumor tissue, fat, air, or foreign substances Since it is at times difficult to establish that the occluding material has not formed *in situ*, a demonstrable source and the integrity of the underlying artery should be sought An electrocardiogram typical of recent coronary occlusion can sometimes be obtained

Embolization to a coronary artery of cardiac valvular vegetations is particularly common in subacute bacterial endocarditis[33] Usually, an aortic valve is involved, in 1 case, the free end of a thrombotic vegetation which at the other end was still attached to its origin on an aortic valve, plugged a coronary artery and caused death Microscopic emboli are common, and multiple gross emboli have been reported Changes in the myocardium are common petechial hemorrahages, scarring, recently infarcted areas, and even perforation of the myocardium

Displaced fragments of thrombi arising in peripheral veins may be carried to the coronary arteries by paradoxic embolization or by other means, they may arise from atheromatous aortic ulcers, or they may have their origin in a thrombotic fragment in the coronary arterial tree In 1 case, there was a thrombus in the proximal portion of the circumflex branch of the right coronary artery from which a fragment had broken off and lodged at the point where the posterior descending branch leaves the right circumflex branch.[201] In another case, that of an infant, the source could not be demonstrated but it was thought that the fragment might have come from an umbilical vein thrombus[222] In a third case, a coronary embolism arose from a tuberculous focus in a pulmonary vein.[146]

In 1 reported case, tumor tissue was carried to the coronary artery by paradoxic embolism[202]

Fat embolism, while probably not as important as fat embolism elsewhere, should not be overlooked as a possible cause of death after trauma It produces "streak-like" hemorrhages in the myocardium, and fat droplets are demonstrable microscopically in the small vessels

Foreign material, accidentally injected into a vein, may plug a coronary artery, zinc

peroxide was found in the coronary artery in 1 case.[239]

Paradoxic embolism has been reported in 4 *cases;*[114, 232, 263] *in 1 case, the pulmonary* circulation was not depleted and there was no evident change in the right-left heart pressure relationship, factors which some believe to be necessary for the production of this type of embolism.

Air embolism has been produced experimentally.[197]

Various theories have been advanced to explain the rarity of embolism in the coronary arteries. Marie[140] believed that a possible reason was the great difference in the calibers of the aorta and the coronary arteries. Pavell and Benson[174] thought that the right-angled departure of the arteries made it difficult for emboli to lodge there. Saphir[201] stated. "The various eddies at the mouths of the coronary arteries as produced by systole and diastole, and also the peculiar flow into the coronary vessels during systole and diastole might explain the rare involvement by emboli of the mouths of the blood current in the aorta and the fact that most coronary filling is in diastole might be factors"

Since DeNavasquez[47] showed that minute emboli frequently enter the coronary arteries, *Chipps*[35] *believed that the factor determining* the rarity of gross coronary embolism is the size of the emboli. Emboli sufficiently large to occlude the main coronary branches are probably much rarer than minute emboli in bacterial endocarditis

THROMBOSIS There seems little doubt that thrombosis effects changes in the vessel wall, as originally suggested by Rokitansky. Duguid even thought that thrombosis plays a role in the pathogenesis of coronary atherosclerosis It seems entirely possible that such systemic diseases as sickle cell anemia and polycythemia vera, which cause sludging and thrombosis in small arteries, may affect the arterial walls with the passage of time.

NEOPLASM A cardiac tumor may press on the coronary arteries or invade them, in either case causing occlusion Thus, in 1 case the right coronary artery was completely occluded,[7] and in another the left circumflex artery was partially occluded by pressure from surrounding tumor tissue.[69] Or the coronary arteries may be involved in metastatic extension of breast cancer.[178]

VARIATIONS AND ANOMALIES OF CARDIAC BLOOD VESSELS

The coronary arteries exhibit great variability, especially in the distribution of individual branches, but there is no agreement about the incidence of anomalies Figures vary from a fraction of 1 per cent to 40 per cent This wide range is largely the result of differences in classification or nomenclature. Accessory coronary arteries or twigs frequently arise from the aorta, these may be considered variations rather than anomalies, with a resultant difference in reported incidence. Thus, one investigator[226] found such accessory vessels in 40 per cent of hearts. Anomalies of sufficient degree to be clinically important, on the other hand, are extremely rare. In 6,800 postmortem examinations, only 4 anomalies were found of sufficient extent to warrant mention[23]

The anomalies of the cardiac blood vessels are as follows.

- Anomalous Origin
  - From common arterial trunk *or* branches
  - From pulmonary artery origin
    - left coronary artery
    - right coronary artery
    - both coronary arteries
    - accessory coronary artery
  - From combined aorta and pulmonary artery
  - Abnormal origin from normal aorta
    - Unusually high origin
    - Origin from same sinus
  - From cardiac ventricle
- Anomalous Number
  - Single artery
  - *Multiple arteries*
    - Arising from aorta
    - Arising from pulmonary trunk
- Anomalous Distribution
  - In myocardium
  - Abnormal communications with cavities
  - Abnormal communications with arteries
  - Abnormal communications with veins
- Anomalous Size

Congenital Aneurysm
- Dilatation at branching points
- Of sinuses of Valsalva
- Of coronary artery branches

Anomalous Veins
- Anomalous drainage of coronary sinus
- Atresia of coronary sinus ostium
- Anomalous drainage of pulmonary veins into coronary sinus

ANOMALIES OF ORIGIN These may be classified as (*1*) common arterial trunk or branches; (*2*) origin from the pulmonary artery; (*3*) abnormal origin from normal aorta; (*4*) origin from a cardiac ventricle.

(*1*) When there is a single arterial trunk, there is usually a single coronary artery The branches may arise anywhere, *e g.*, aortic arch, innominate artery, carotid artery; occasionally, the branches may arise from their usual position, in or near the sinuses at the origin of the main vessel.

(*2*) The primitive endothelial buds, which later form the coronary arteries, develop before the common arterial trunk is divided by the spiral septum into the aorta and pulmonary artery.[216] A displacement of the spiral septum or of the endothelial buds may result in the enclosure of the buds within the pulmonary artery. A number of variants of this anomaly have been identified

(*a*) Over 30 cases of the left coronary artery arising from the pulmonary artery (Bland-White-Garland syndrome) have been reported.[15, 49, 70, 80, 94, 136, 225, 208] In nearly all cases, the anomalous artery arose from the pulmonary trunk, 1 case has been described in which the origin was the right pulmonary artery In 20 who lived to adult life without symptoms, definite collateral circulation between the main coronary arteries was found. In some of the cases there were sinusoids in the myocardium and epicardium A report on 1 case makes a distinction between infantile and adult types, the latter having extremely dilated coronary arteries, probably an adaptation permitting survival.[94] A report on 2 additional cases of anomalous origin of the left coronary artery from the pulmonary trunk discusses the possible relationship of this anomaly to endocardial fibroelastosis [15]

Many cases are fatal during the first year of life. The heart is greatly enlarged. The T waves are usually inverted in the limb leads, with low voltage and normal axis deviation.[23] There is no cyanosis, nor are murmurs heard until failure sets in After several weeks of life without symptoms, the patient may show difficulty in taking his feedings, which are interrupted by crying spells probably indicative of anginal pain.

(*b*) The anomalous origin of the right coronary artery from the pulmonary artery is rarer and more benign than that of the left.[43]

(*c*) Only a few cases of the anomalous origin of both coronary arteries arising from the pulmonary artery have been reported None survived early infancy. The anomaly has been seen in association with the tetralogy of Fallot [219]

(*d*) An accessory coronary artery arising from the pulmonary artery is seen occasionally, it is of no clinical importance

(*e*) A coronary artery arising from both the aorta and the pulmonary artery has been reported in 2 cases [219] In each case, the aorta originated from both ventricles via a high ventricular septal defect; the pulmonary artery was completely atresic at its origin, with its distal portion being supplied by a large branch of the left coronary artery in one case and of the right coronary artery in the other. This is analogous to the situation created by the Blalock operation The anomaly is explained by the assumption that faulty rotation of the aortopulmonic septum results in the splitting of one of the endothelial buds, so that the coronary artery has two origins—one from the aorta and the other in the pulmonary artery

(*3*) Abnormal origin from a normal aorta may take the form of an unusually high origin or of an origin from the same sinus. An unusually high origin was found in 80 of 1,000 autopsies.[233] Usually, the right coronary artery is the higher one It may rise as high as 18 mm above the level of the free edge of the cusp More rarely, the coronary vessels may arise at unusually low levels When both arteries have their origin in the same sinus, there is no functional change in the heart, the variations are found accidentally in persons who have had no symptoms

(*4*) Origin of a coronary artery from a cardiac ventricle has been reported in 2 cases[4, 259] In one, a large coronary artery arose directly from the right ventricular wall,[27] the infant died after 4 days of life

ANOMALIES OF NUMBER These may be either the absence of a coronary artery, or the presence of *multiple arteries*

A single coronary artery has been reported in 46 cases, 29 in adults, one of whom was a woman 60 years old[214, 224] Most often, this means merely a common aortic origin of both coronary arteries, the single artery then quickly dividing into branches which correspond anatomically and functionally to normal coronary arteries[214] A true single coronary artery is a rare anomaly[142] A recent report collected 22 cases from the literature and added 9 cases, the left coronary artery was missing in 17 cases, the right, in 11, the identity of the missing artery in 3 cases was not evident from the description[193]

Multiple arteries usually arise from the aorta, and may number three, and more rarely four The supplementary vessels are small, and may be easily overlooked, they are probably fairly common[2-9] They occur in either side, but more often on the right The left circumflex artery may arise independently from the aorta.[6] In a series of 100 hearts, multiple vessels were found in 40. The death of a 17 year old boy was reported from infarction after occlusion of one of two left coronary arteries.[152]

Multiple arteries arising from the pulmonary are a rare anomaly.

ANOMALIES OF DISTRIBUTION They may occur: (*1*) in the myocardium, for example the left circumflex artery giving rise to the posterior descending artery; (*2*) as abnormal communications with the cavities, for example a coronary vessel connecting the aorta with the left ventricle. with the direction of blood flow from the ventricle to the aorta, (*3*) as abnormal communications with arteries; and (*4*) as abnormal communications with veins, for example, a communication between the right coronary artery and the coronary sinus, with aneurysmal dilatation of both[105]

ANOMALIES OF SIZE Occasionally, there are striking variations in the caliber of normal vessels In some cases the arterial system is uniformly hypoplastic.[190] In a series of 81 autopsies, 4 hearts had coronary arteries of uniformly small caliber, only 1 of these had coronary disease, 3 of the hearts were hypertrophied.

ANEURYSM Three types of congenital aneurysm are usually recognized[119] (*1*) dilatation at branching points, analogous to "berry aneurysms of the brain, (*2*) aneurysm of the sinuses of Valsalva, often associated with congenital defects of the aortic valves,[170] and (*3*) dilatation of branches of the coronary arteries, reported in 6 cases[35, 131] A fourth category, (*4*) arteriovenous aneurysm, may be added, 3 cases have been reported in the English literature, in 1 case, that of a 58 year old woman, the clinical features were of a large patent ductus arteriosus but a congenital communication between the left circumflex artery and the coronary sinus was found at autopsy[46]

ANOMALIES OF VEINS Variations in the venous system of the heart are common, and often can easily be explained on embryologic grounds.[101] Only 6 cases have been described in which the coronary sinuses opened directly into the left auricle, without other abnormalities[64] The coronary sinus, if anomalous, usually drains into a persistent left superior vena cava which itself may empty into the left auricle or into another major vein. Coronary venous drainage into a common ventricle has been described[154] There may be anatomic variations in the *orifice of the coronary sinus*[109] *Atresia of* the ostium of the coronary sinus is rare. Anomalous drainage of the pulmonary veins into the coronary sinus has been reported[277]

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CHAPTER 3

Geographic and Ethnic Factors

THE GEOGRAPHIC distribution of coronary disease, insofar as it can be determined from the meager and less than accurate data available, supports somewhat the theory that food habits may have some bearing on the disease Most recent attention has been directed to racial variations in blood lipids and their relation to dietary habits and the incidence of coronary disease Hereditary and genetic factors, already mentioned, are receiving scant attention in the current literature Nevertheless, they are important and interest in them will doubtless be revived. Navajo Indians have little coronary disease, although their diet is typically American and a genetic factor is likely in their immunity [31]

On the whole, the evidence about the differences in cholesterol intake is that for any group as a whole the ingestion and the cholesterol blood level correlate roughly. The correlation between dietary habits and coronary disease incidence seems to be better established. However, whether average blood cholesterol values for a group can be considered "normal" is open to doubt It has been pointed out that the high animal fat intake of the population of the United States may account for the present national average of serum cholesterol [16]

Mortality from all forms of heart disease combined is considerably higher in the nonwhite than in the white population in our country, and the average age at death from coronary disease has been given as 56.1 years for Negroes and 62.2 for the white population [26] Table 4 gives the experience of the Metropolitan Life Insurance Company.[29] However, the incidence of coronary disease in the Negro here is believed to be comparatively low. In Canada, the mortality rate from "angina pectoris and coronary disease" has been reported to be much lower in Negroes than in white persons [32] In a postmortem study of an Army series, only 3.8 per cent of the cases were Negroes, as opposed to the 10 per cent of Negroes in the U.S. Army [43] In Louisiana, the incidence rate was somewhat lower among Negroes than in the white population [20] Coronary thrombosis was said to occur one-fourth as often in the Negro as in the white;[33] the Negro has an "apparent resistance" to myocardial infarction [44] In view of the Negro's susceptibility to hypertension, the figures just cited are noteworthy.[42] No racial differences have been found in the incidence of advanced coronary sclerosis or infarction in persons with hypertension.

The clinical and pathologic features of coronary disease in Negroes are reported by

TABLE 4 MORTALITY RATES, CORONARY ARTERY DISEASE, 1945-1949*[29]

Age (yr)	Men		Women	
	White	Negro	White	Negro
25–34	7 4	6 8	2.2	4.9
35–44	72 5	38 7	11 0	25 0
45–54	254 7	126 2	48 4	69.1
55–64	508 7	241.7	155 7	139 2
65–74	829 9	410 5	393 4	269 3

* Data relate to deaths classified under category 94A of the *International List of Causes of Death*, Fifth Revision

some to be identical with those in white patients,[43] while others have suggested that coronary disease in Negroes is apt to be more severe than in white persons.

Various causes may be responsible for the apparent racial differences: (*1*) Death of the Negro at an earlier age[33, 44] The economically depressed state of a large part of the Negro population in the United States, the physically dangerous types of work, and poverty with its attendant ills all tend to shorten life so that the "age of infarction" is reached by smaller numbers But in Louisville, coronary occlusion was found to occur as often in the indigent Negro below the age of 70 as in the indigent white.[21] (*2*) If coronary disease is in part a disease of overnutrition, the Negro's undernutrition may be a factor in his relative immunity Other reasons advanced in explanation of alleged racial differences are (*3*) Anatomic differences, thus, in the Bantu, the posterior heart wall is reported to be more richly endowed with blood vessels than the heart of the white European.[5] (*4*) Less rapid aging of the coronary arteries (in contrast to the renal arteries), *i e.*, less fraying of the lamina elastica interna.[17] (*5*) Dilatation of the coronary collateral circulation, due to hypertension (which is more frequent in the Negro);[21] this explanation can be accepted only with great wariness

T. M Smith,[37] in a thorough study of coronary disease in the Negro, found among 400 patients in the Provident Hospital, Chicago, 155 with coronary disease. He concluded that the incidence is about the same in both racial groups, and that pain occurs just as often His investigation satisfactorily refuted the contention that dyspnea rather that pain is the most prominent symptom in the Negro patient It is noteworthy that almost half of the patients in his series were women McVay and Keil report considerably less coronary disease among Negro men than among white men; this difference does not exist among the women in their series. They feel that angina is not as conspicuous a symptom among Negroes[20a]

In summary, it seems just possible that Negroes are less susceptible to coronary disease, but the evidence for any significant difference is far from convincing

In Africa, the Negroes of Kenya are said to have little arteriosclerosis.[10] The incidence of severe arteriosclerosis in the Bantus is significantly lower than that found in the hospital populations of the United States or Denmark[13] The blood cholesterol levels of the older Bantus (over age 40) are lower than of the Europeans in South Africa, this difference is not found in the young Bantus[41] The fat content of the Bantu diet represents 16 per cent of their total caloric intake, in the "Negro" diet, fats make up 25 per cent of the calories, but in the diet of the poorer white population fats amount to about 35 per cent, and as the economic level rises the percentage increases correspondingly, accompanied by a greater incidence of atheroma.[21]

In Hawaii, coronary disease is found among all races; it seems to be more common among Hawaiians who are overweight, eat much sugar and fat, and in whom diabetes is frequent, and is comparatively rare among the lean, active Japanese whose diet contains little fat[15]

In the Orient, lesions of the coronary arteries are of rare occurrence Coronary disease is rare in the Okinawans,[8, 39] who are closely related to the Japanese. From the available data, it may be inferred that coronary disease seldom occurs in the Chinese,[31, 35, 38] their diet is low in protein and animal fat Chinese living in the United States, however, whose diet more closely approaches the American one, are not as immune to atheroma; this would seem to point to a dietary rather than a genetic factor as the determinant of racial susceptibility.[33] A report on 10,000 Japanese autopsies states that the incidence of severe coronary disease is only about a tenth of that in the United States[25] In this case, too, there is reason to believe that among the Japanese of American birth (Nisei) there is a greater incidence of atheromatosis than in Japan.[22] Luminal narrowing due to atheroma is far less common in young Japanese than in American soldiers of the same age (under 30) killed in action There is a much lower rate of "cardiovascular thrombosis" among the natives of Ceylon than in the European residents there[7, 8] The nomadic Khirgis plainsmen, who consume unusually

large quantities of milk and meat, have a high incidence of obesity, early and extensive atherosclerosis, apoplexy, and arcus senilis[25]

In the Phillipine Islands, the villagers, who are rice eaters, seldom have coronary disease; but in Manila the members of the mercantile class, whose diet includes dairy products, do have coronary disease[9]

Among the Indians of Peru, so far as is known, myocardial infarction does not occur, that is not the case among other ethnic groups in Lima[34] An exhaustive study[28] of the Guatemalan Indians revealed that serum cholesterol of the rural Indians of both sexes was lower than those of the urban Indians or of the North American Indians The rural Guatemalan Indians subsist largely on a vegetarian diet, and consume far less protein, fat, cholesterol, and total calories than the other two groups. The β-lipoproteins were only slightly and irregularly lower in the rural males than in the urban males, in the females, this fraction was often higher in the Guatemalan Indians than in the North American ones

The available information regarding atheroma in the Eskimoes, some of whom at least consume large quantities of animal fat, is scanty and confusing[8, 14, 36, 40] Nothing definite is known about the Eskimo dietary, and autopsy data on their coronary arteries is lacking Statements on the incidence of atheroma, therefore are based entirely on indirect evidence

Coronary disease seems to be somewhat more common among Jews than among their neighbors Of 100 young adult patients in the Boston area, 27 per cent were Jewish,[14] since this is about double the percentage of the total Jewish population in that area, the figures are significant The incidence of diabetes, a frequent precursor of coronary disease, is also high in Jews In Israel, it has been noted that the incidence of coronary disease among Oriental Jews is not as great as among those coming from Western Europe; while obesity is probably less common in the former, their diet probably contains just as much cholesterol[11]

In New York, 35 per cent of the caloric intake is derived from fat, both in the Jewish and Italian dietary, but the animal fat content of the Jewish diet is 10 per cent higher. Hypercholesterolemia was found in 5 2 per cent of a group of Italian workers, and in 14 per cent of a similar group of Jewish workers, the incidence of coronary disease in the two groups with hypercholesterolemia was about the same, but in two groups with normal cholesterol levels the incidence was 6.4 per cent in the Italian and 15 per cent in the Jewish group.[13]

Keys and co-workers[23] have studied the diets and blood lipids of widely varied groups, including business and professional men in Minnesota, soldiers in the U.S. Army, Neopolitans, Swedes, and Spaniards of varying income and activity, Bantus and Europeans in South Africa, and Londoners employed in light industry They found a direct relation between the dietary fat content and the serum levels of total cholesterol and β-lipoproteins in healthy men, this relation was more marked in the midd'e-aged than in the young In areas where diets were high in fat content (40 per cent of the calories), the average cholesterol concentration was 25 to 50 per cent greater than in where the dietary fat intake was low (20 per cent or less of the calories)

Coronary disease decreased in Norway and Sweden during World War II, when fats and eggs were in short supply, and rose again after the war, when these foods were once more plentiful. These observations confirm findings during World War I in Central Europe[1, 2] The incidence of coronary sclerosis in Germany during the years 1945 to 1948, when nutrition was deficient, and from 1950 to 1953, when food supplies were adequate, was about the same, but the number of cases of infarction increased sharply during the latter period, differences in food intake may have been the decisive factor in this increase, although other factors, such as increased cigaret smoking, may also have played a part[30]

The incidence of coronary disease U S Army personnel was higher than in the British army, whose consumption of eggs, butter, ice cream, milk, and cream was much lower than that of our soldiers[9]

From the data, it would seem that the so-called geographic and ethnic factors are

in reality not geographic or ethnic but economic and cultural The availability of high-cholesterol foods, and the economic status and food habits of various population groups must be taken into account in studying the incidence of coronary disease and the correlation of its various components

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CHAPTER 4

Lipid Metabolism

CORONARY SCLEROSIS, like other forms of arteriosclerosis, has long been pessimistically regarded as a degenerative disease about which nothing could be done, as an inevitable concomitant of the aging process. Today, it seems much more reasonable to consider atherosclerosis an extremely complex disease in which senescence plays only a part, a metabolic disorder of highly complex origin, probably episodic in character, but which is in some manner intimately connected with the way the body metabolizes its lipids. Other factors are discussed in Chapters 2, 3, and 5. Although our knowledge of this phase of coronary sclerosis is far from complete, and the therapeutic implications are necessarily premature, the concept of this process as a metabolic disease is a useful, probably sound, working hypothesis.

Coronary sclerosis has afflicted man for many centuries, but it was only a hundred years ago that the essential lesion in what is now called atheromatosis was demonstrated by Vogel to consist largely of lipid material. Interest then lapsed until the beginning of our century, when Windaus confirmed Vogel's finding's and Anitschkow[7] produced the lesion by feeding cholesterol to rabbits. Interest in the subject revived as a result of investigations by Timothy Leary and others. Investigative activity is now widespread.

What is at present known with reasonable certainty about lipid metabolism? It is now certain that: (*1*) fat metabolism is intimately connected with atheroma; (*2*) atheroma in man contains lipid material, (*3*) lesions closely resembling those of man can be produced experimentally in some animals; and (*4*) means have been found to prevent and even reverse these experimental changes. For the rest, the literature is inconclusive.

BLOOD LIPIDS

The term "blood lipids" is generally applied to a heterogeneous class comprising all the fatty substances found in the blood, grouped together despite their dissimilarities because of similar solubilities—they are all biologic materials extractable by fat solvents. The most important of the blood lipids are the neutral fats, the phospholipids, the cerebrosides, and cholesterol. In the postabsorptive state, the blood normally contains on the average some 500 mg. of lipids per 100 ml.;[116] in pregnancy, in persons of pyknic habitus, and in the elderly of both sexes, the figure is somewhat higher. No seasonal variation has been found. A small, variable portion of the blood lipids is in the form of microscopically visible droplets or chylomicrons, but the bulk of the lipids is colloidally dispersed and invisible.

PHOSPHOLIPIDS

Also commonly known as phosphatides, the phospholipids are composed of about 80 per cent lecithin, 15 per cent sphingomyelin, and 3 to 8 per cent cephalin. The two features common to all phospholipids are: (*1*) all contain a nitrogenous base, and (*2*) all yield on complete hydrolysis inorganic phosphate, among other substances. Over 80 per cent of phospholipids contain choline. In the presence of fatty acids, they are readily synthesized in all tissues. Normal fasting plasma contains about 200 mg. per 100 ml.

CEREBROSIDES

These lipids contain no phosphorus and on hydrolysis yield a hexose sugar. They are widely distributed in cells but are not important in blood.

TRIGLYCERIDES (NEUTRAL FATS), FATTY ACIDS

100 ml. of normal fasting blood contains 225 mg ($\pm$140) of *triglycerides*, including cerebrosides. It is probably only the increase in these lipids which causes opalescence of milky serum.[6]

The fatty acids which are really "free" in solution are better called "unesterified" or "non-esterified" acids. They form a small percentage of the blood fatty acids which are firmly, though reversibly, bound to the blood proteins. Heparin, probably acting through a lipase, the "clearing factor", hydrolyzes the triglycerides of chylomicrons to produce these unesterified fatty acids Fasting, fat ingestion, epinephrine injection cause rises in the blood level of these acids and carbohydrate feeding causes a fall. It may be that this lipid fraction has its origin in adipose stores and is concerned primarily with the supply of fats to tissues for oxidative metabolism.[214]

CHOLESTEROL

(Fig 19). This lipid is the chief protoplasmic sterol of animals; the plant sterols

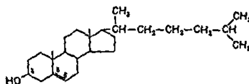


FIG. 19. Cholesterol.

are closely related, but are not cholesterol The plasma concentration of cholesterol is apparently higher in man than in other mammals (Fig 20).[2] It is noteworthy that spontaneous atherosclerosis is rare in animals, an exception is the ground squirrel, whose cholesterol levels are comparable to those of man, and in whom spontaneous atheroma has been found.[17]

Normal fasting blood contains 200 mg. ($\pm$50) of cholesterol per 100 ml, composed of 55 mg. ($\pm$15) free cholesterol and 145 mg. ($\pm$35) cholesterol esters. The blood level rises slightly in some people, not all, and variably with advancing age. Cholesterol is normally stored by the body, although related in part to cholesterol ingestion, storage is mainly governed by endogenous factors which are not yet clearly known

Some of the cholesterol in the body is synthesized, the rest is ingested in the food *In vitro*, cholesterol can be synthesized from acetate, with squalene probably as an intermediate metabolite, whether this is the process *in vivo* is still undetermined About 4 Gm of total steroids—cholesterol, bile acids, and sex hormones—are synthesized daily, in large part by the liver, with cholesterol accounting for about half of the total. Cholesterol ingestion probably depresses its synthesis, thus tending to keep it at a contant level in the body

The intermediate metabolism of cholesterol, reviewed in detail by Bloch,[15] is still largely unknown, most of it is apparently degraded and not excreted About 1 Gm of total sterol is excreted daily in the feces, 100 to 150 mg. via the skin, and trace amounts in the urine It has been suggested that adequate formation of certain phospholipids is necessary for normal cholesterol metabolism, lecithin (phosphatidyl choline) being the essential substance.[ed] The differences in species susceptibility to cholesterol-induced atheroma might thus be related to species differences in the capacity to form this compound

LIPOPROTEINS

The cholesterol in plasma, whether in free or esterified form, is always bound to protein. The lipoproteins are giant molecules composed of triglycerides, phospholipids, cholesterol, and protein in varying combinations

ROLE IN ATHEROGENESIS

Evidence is accumulating of a relationship between changes in the plasma content of lipids and atherosclerosis, but there is as yet no absolute proof that these changes cause the sclerosis.

CHOLESTEROL METABOLISM

A direct link between cholesterol metabolism and atheroma formation in man has so far not been found, all the evidence is still circumstantial While the incidence of coronary disease in persons with elevated

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and there is no unusual tendency to coronary disease.[3] On the other hand, in myocardial infarction the cholesterol-phospholipid ratio is increased, as compared to matched controls.[29, 30] Quite possibly, the importance of the cholesterol-phospholipid ratio derives from the varying amounts of cholesterol in the α- and β-lipoproteins. The cholesterol–α_1-lipoprotein ratio, it has been suggested, is the best biochemical indication of an atherogenic tendency.[34] While the balance between the lipid fractions may be important, some reports would seem to indicate that the total cholesterol–phospholipid ratio is no more important than the now discredited total cholesterol level.[36, 45]

2. ALTERED HEPARIN LEVELS. Heparin, or heparinoid substances, are a normal blood constituent. In the presence of advanced atherosclerosis, the concentration of these substances in the blood decreases,[4] as well as the number of mast cells in the tissues.[19, 41] Mast cells are numerous in early atheromatous patches.[90] Furthermore, in these patients, the clearing of postprandial hyperlipemia by heparin is delayed.[16]

3. ALTERATIONS IN BLOOD LIPOPROTEINS. As has already been mentioned, the blood lipids (cholesterol, triglycerides, phospholipids) are bound to protein and form larger molecules of varying size and composition. Since experimental evidence indicates that the size of a particle in the blood stream determines whether it penetrates the intima, and, if it does, whether it is retained or passed on into the blood stream, the size of lipid molecules may be of considerable importance.

A study of the effect of various substances (polyvinyl alcohol, methyl cellulose, acacia, pectin) on vessel walls revealed that the size and possibly the shape of the large molecules in these substances facilitates their uptake and retention in vascular walls, producing lesions resembling atherosclerosis.[44] Injection of heated pectin, which reduces the size of its molecules, did not cause damage of vessel walls in rabbits and dogs. In another study which used variously sized carbon particles, the largest particles did not penetrate the intima at all, the smallest particles passed through the arterial wall, and the particles of intermediate size penetrated the wall and were trapped intramurally.[28] In a third study, hyperlipemic rabbit serum was separated so that the large-sized lipoprotein particles were in the upper layer; injection of the lower layer only, which contained the smaller particles, proved to be atherogenic in normal rabbits.[17] Despite high cholesterol levels, no atheroma develops in cholesterol-fed, alloxan-diabetic rabbits; a large proportion of this cholesterol is contained in lipoprotein particles larger than Sf 100.[55] An aortic perfusion technic in guinea pigs demonstrated that lipid molecules of a particular size only were deposited in vessel walls.[121]

LIPOPROTEIN CLASSIFICATION

The blood lipoproteins may be classified in several ways: (*1*) by chemical fractionation; (*2*) by analytic ultracentrifugation; and (*3*) by electrophoresis. With certain exceptions, all three methods give results which correlate with each other reasonably well, and which, clinically speaking, point in the same direction.

CHEMICAL FRACTIONATION. Extensive chemical studies of the lipoproteins have been based on Cohn's fractionation method #10.[24, 81, 87, 93] Of the total plasma cholesterol, 25 per cent is contained in the α-lipoproteins, which are bound to α-globulin, while 75 per cent is in the β-lipoproteins.[61]

The α-lipoproteins are contained in the Cohn fractions IV+V+VI, and migrate with the mobility of α-globulins.[24] Their molecular weight is about 200,000, and they contain more protein (50 to 60 per cent) than the β-lipoproteins (25 per cent). The cholesterol–phospholipid ratio is about 0.5.

The β-lipoproteins are contained in the Cohn fractions I+III. They are large spherical molecules weighing about 1,200,000, containing large amounts of water and important amounts of lecithin. The cholesterol–phospholipid ratio is about 1.3. These molecules therefore contain less phospholipid and more cholesterol than the molecules of the α-lipoproteins.

There is mounting evidence that the dominant factor in atherogenesis may be a rela-

tive excess of the β-lipoproteins, in other words, a decrease in the ratio of α- to β-lipoprotein

Two thirds of the circulating cholesterol in young women is in the β-lipoprotein fraction, whereas in young men it is three fourths of the cholesterol. With advancing age, the cholesterol in the α-lipoprotein fraction increases, that in the β-lipoprotein fraction decreases, and the sex difference disappears The cholesterol content of the α-lipoprotein fraction is uniformly low in atherosclerosis, nephrosis, and familial hypercholesterolemia In myxedema, the mean total lipid, total cholesterol, phospholipids, and β-lipoprotein are all significantly increased [47] In biliary obstruction, a condition in which hyperlipemia occurs regularly and often severely, there is no tendency to coronary disease In this condition, abnormal lipoproteins have been found, when determined by centrifugation and electrophoresis, they seem to be β-lipoproteins, but when determined by chemical fractionation methods they appear in Cohn's fractions IV+V+VI, where the α-lipoproteins are located.

In patients with known coronary disease, a relative and absolute decrease in the plasma albumin and α-lipoprotein and an increase in the β-lipoprotein have been found These changes occur even in the absence of hypercholesterolemia or of a significant rise in the cholesterol–phospholipid ratio.

Postmortem study of 157 cases of sudden death due to violence or natural causes has contributed valuable information [102] A highly significant ($p<0.1$) correlation between lipids and atheroma was revealed when the serum β-lipoprotein content, the somatotype, and the degree of aortic and coronary sclerosis were compared, the over-all correlation between the β-lipoprotein level and the atherosclerosis was 84 per cent The correlation for the ectomorphic male was 60 per cent, for the other groups 90 to 92 per cent. These data are particularly meaningful because clinical diagnosis, which is always untrustworthy, was not a factor in determining the degree of coronary sclerosis From the evidence, it would seem that, with the exception of the ectomorphic male, any person with a high β-lipoprotein level should be regarded as a potential victim of atheroma.

ULTRACENTRIFUGATION At high centrifugation speeds, lipoprotein fractions separate according to their densities. Gofman, who employed this method for exhaustive studies of the lipoproteins, both popularized and made the technic useful, and his nomenclature is now widely used, it is based on the Svedberg unit. The fractions obtained were given numbers according to their flotation constants (Sf), which are analogous to the sedimentation constants of the more usual proteins.

The lipoproteins can thus be graded by molecular size according to flotation rates ranging from 2 to 40,000 Gofman divided the lipoproteins into four groups, using Svedberg units as a measure of size. (*1*) Larger than 100 Sf units; these are the chylomicrons found in alimentary lipemia with neutral fat comprising the major lipid of the molecules; (*2*) Sf units 20 to 100, these contain some cholesterol and constitute the largest fraction in alimentary lipemia. (*3*) Sf units 10 to 20; these have a molecular weight of 3,000,000. This group may be further subdivided into three groups, each containing about 30 per cent cholesterol (*4*) Sf units 3 to 8; this group contains the major portion of the blood cholesterol

Some hold, although it has not been incontrovertibly established, that under normal conditions the lipoprotein molecule begins as a chylomicron (Sf over 75) and then undergoes a stepwise breakdown to smaller particles as it loses its neutral fat. Heparin seems to play a role in this process

Gofman at first thought that the intermediate sized lipoprotein particles (Sf 12 to 20) were of critical importance in atherosclerosis in man. The serum concentration of these lipoproteins is low in children, in young women, and in animal species in which spontaneous atheroma does not occur; in rabbits, these lipoproteins appear only after several weeks of a high-cholesterol diet, and atheroma becomes evident only then.[33] In patients with diabetes, nephrosis, and myocardial infarction, the Sf 12 to 20 lipoproteins are increased.

The atherogenic group of lipoproteins has recently been enlarged by Gofman to include the Sf 20 to 100 class After a meal rich in fats, there is a great increase in this class,

and especially in the Sf 35 to 100 lipoproteins. In Page's[82] opinion, this extension considerably weakens Gofman's original hypothesis about the atherogenic specificity of the Sf 12 to 20 lipoproteins. As Page points out: "The core of the problem is whether these restricted classes of serum lipoproteins are, in fact, the ones which signal developing atheroma and whether they are the ones which appear in the blood vessels as atheromatous deposit."

Molecules of a particular Sf class cannot be regarded as of uniform chemical composition.[112] The ultracentrifuge merely demonstrates how a given molecule behaves in an artificial field of gravity, and it is a physical, not a chemical, constant that is measured. The chemical nature of the molecules within any given Sf class may vary from person to person, or from time to time in the same individual

Whether or not the Gofman "particles" are the cause of atheroma, Gofman performed a signal service in bringing this phase of lipid metabolism and atherogenesis to popular attention The problem is now being carefully studied by the United States Health Service at Bethesda by means of co-operative follow-up by four laboratories of 12,000 persons whose lipoprotein levels had earlier been established

Ultracentrifugation using a somewhat higher density (1 21) than that employed by Gofman is preferred by Lewis and Page.[87] By combining this method with electrophoretic determinations, they believe that a somewhat better picture of the serum lipoprotein composition is obtained than by either method alone.

ELECTROPHORESIS The lipoproteins have also been studied by the migration of their proteins when subjected to paper or zone electrophoresis[2, 77, 80, 98, 107] This method has the advantage of being cheaper and simpler than the other methods just described, but it is only just beginning to lend itself to accurate quantitative analysis[66] It has been shown by electrophoresis that the α-lipoprotein–β-lipoprotein ratio is significantly lower than normal in the presence of established coronary sclerosis[11, 80]

DIET, BLOOD LIPIDS, AND ATHEROGENESIS

Were the vexing problems of the effect of diet solved, uncertainties in the treatment of coronary disease would be clarified and considerable information about the cause of atheroma supplied But information on this subject is still so fluid and unsystematized that one looks in vain for definite answers At best, one finds the unsettled opinions of many workers from which a tentative selection can be made. No matter what school of thought is selected, much textual support can be found for it.

Coronary atheroma is a disease which is caused by many factors, all of which are discussed elsewhere in this book genetic factors, physical and mental activity, infections, diabetes, smoking, hypertension, etc may all play some part It is our present concept that disturbances in lipid metabolism constitute an important etiologic factor, probably the dominant one. It is highly likely that the other causative influences mentioned harm the body by way of its handling of lipids In any event, although the case is still far from conclusive, the bulk of the evidence is that the diet is intimately associated with derangements in the blood lipids and that these disorders, in turn, are responsible for the development of coronary atheroma. There is even some suggestion that the final step, myocardial infarction from thrombosis at the site of atheroma, may be determined by defects in lipid metabolism although this is still a subject we know little about. The reader is cautioned therefore that the author, although he proposes to give considerable attention to diet at this point, is far from considering this the only etiologic agent in atheroma

DIETARY CHOLESTEROL RESTRICTION

The average consumption of cholesterol in this country is probably less than 1 Gm a day, although the proportion of calories (41 per cent) supplied by fat is higher than in any known population group in the world Cholesterol consumption in the United States has been estimated to range between 200 and 800 mg daily per capita[67] In my experience the upper limit is certainly too low for some groups, for example, the average of 50 [illegible]

men diets for New York Jews was closer to 1000 mg., and the highest daily intake, 1500 mg., in my knowledge was that of a Middle Westerner who ate vast quantities of meat. In contrast, the cholesterol consumption of the Italian population here is much smaller because so much of their dietary fat is in the form of olive oil.

What effect reducing the dietary cholesterol alone has on the level of serum cholesterol is still a matter of controversy. Most clinical reports are based on experiments in which other dietary constituents (total fat, proteins) and caloric intake are also restricted, and therefore cannot be accepted as conclusive. Some workers find that animal fat restriction does not affect the serum cholesterol.[40, 73] There is somewhat more evidence that such diets will decrease the level of blood cholesterol and the "atherogenic" lipoproteins.[4, 46, 51, 102, 111, 114] All investigators report that the nature of any given patient's response is unpredictable. This unpredictability is a common finding in almost all human lipid studies. Most recent evidence points to a lowering of the blood lipids when vegetable fats are substituted isocalorically for those of animal origin.[4, 22, 37, 57, 110] The geographic data are presented elsewhere. Certainly, strict vegetarians have lower blood cholesterol levels than vegetarians who eat dairy products, and in both groups the levels are lower than in the general population.[30]

In animals with cholesterol-induced atheroma, it has been amply demonstrated that atherogenesis ceases when cholesterol is withdrawn from the diet and that the vascular lesions may regress in part or completely. To assume, however, that a similar effect obtains *in man is an unjustified conclusion,* although admittedly there is no evidence that it does not. Our knowledge of all the factors concerned, such as the role of endogenous cholesterol, is still so meagre that no definite position can be taken on whether atheroma formation is affected by dietary restriction. There is a little clinical evidence that it may indeed be so.[75a]

Some investigators feel strongly that the crux of the dietary problem is the amount of total dietary fat, regardless of whether it is animal or plant in origin, and that it is necessary to reduce it all to affect the blood lipids beneficially.[40, 52, 73]

ROLE OF UNSATURATED (ESSENTIAL) FATTY ACIDS

Currently, the greatest interest is focussed on the nature of the fatty acids in the dietary fat.

Malmros,[67a] when using corn oil, reduced *the blood level of cholesterol* in patients with familial hypercholesterolemia. Some meticulous and promising studies are those of Ahrens and his staff at the Rockefeller Institute in New York. They find that the substitution of plant fats for animal fats on an isocaloric basis results in a reduction of the levels of blood cholesterol and β-phospholipids whether the initial blood figures in their patients was high or normal. This fall is enhanced by the use of corn oil as the major or exclusive fat. Patients fed on corn oil as the sole fat had no rise in blood cholesterol when 2 Gm. or more of pure cholesterol was added to the diet each day. If all the fat is given as corn oil, the greater the amount of fat ingested, the lower *the blood cholesterol* level. For example, in 49 subjects on a fat-free diet in whom the blood cholesterol decreased 21.4 per cent, a further decrease of 10 to 13.8 per cent occurred when corn oil was added to the diet, addition of butter resulted in a sharp increase in levels.

In the light of this, it is reasonable to wonder whether the structure of the fatty acids involved is responsible for the greater efficacy of some vegetable oils than others. There is growing evidence that the degree of unsaturation may be decisive. Corn oil consists almost entirely of highly unsaturated triglycerides. It contains about 57 per cent of linoleic acid which has a high iodine number, indicating a large degree of unsaturation. When more saturated fats are taken, the blood cholesterol level rises. If cottonseed oil is given, a blood cholesterol figure is reached which rises when the oil is saturated by hydrogenation. Sinclair,[94b] and Bronte-Stewart and associates,[17a] pursuing a similar line of reasoning, argue persuasively for the importance of highly unsaturated "essential fatty acids" (E.F.A.), especially linoleic acid. Diets rich in saturated fatty acids but low in E.F.A. or vitamin B_6 (needed for the conversion of linoleic acid to arachidonic acid) will, Sinclair feels, result in the formation of cholesterol esterified with saturated fatty acids,

a form of cholesterol more likely to be stored in arterial walls as atheroma. Soybean oil, linseed oil, millet seed, and walnut are other sources of unsaturated linolenate

E.F.A may be saturated when fats are hydrogenated or deep fried. The relative immunity, if it exists, of the Eskimo to atheroma despite his high animal fat intake may be because so much of his food is in the form of unsaturated marine fats; on the other hand, whale oil prepared for use in oleomargarine is deodorised, hardened and thereby saturated by hydrogenation An arresting observation is the finding by Sinclair that in experimental animals, males are about five times as susceptible to E F A deficiency as are females.

In this connection, other accessory factors *may be involved in the abnormal lipid metabolism* which may result in atheroma Schroeder points out:

> Vitamin B_6 or pyridoxal phosphate may be involved This ubiquitous coenzyme not only acts as codecarboxylases and cotransaminases but promotes the conversion of linoleate to arachidonate and linolenate to hexaenoate in rats, thereby increasing the unsaturation of partly unsaturated fatty acids Furthermore, deficient states in monkeys result in subintimal lesions microscopically identical with those of early atherosclerosis (providing a locus where lipids are deposited?); and deficient monkeys fed cholesterol exhibit much higher blood-levels than do controls. This heat-labile, light-unstable coenzyme is low in many processed foods, and many dietaries may be marginal during winter seasons. Does a partly deficient man handle linoleate or even oleate less readily than one with adequate amounts of this vitamin?
>
> The second influence is, strange to say, in trace metals Pyridoxal probably requires a trace metal for coenzyme activity; on two decarboxylases that metal is possibly zinc Curran has shown that chromium increases hepatic synthesis of cholesterol and fatty acids in rats by 150%, vanadium depressing synthesis markedly and even reducing aortic lipids by a half in cholesterol fed rabbits Furthermore a chelating agent which is not metabolised, ethylenediamine tetra acetate, reduces plasma-cholesterol markedly and rapidly when given intravenously and often reduces it to Bantu levels" when given orally There are variable but often relatively large amounts of "abnormal" trace elements in American human tissues from all cities studied, with fewer in American stillborn infants and traces to none in the tissues of "raw" African natives (I H Tipton, personal communication) Renal and hepatic cadmium, a decarboxylase inhibitor, chromium, tin, titanium, nickel, and lead are some of the "abnormal" metals found, of which several are apparently the results of "civilisation," showing marked differences in these three groups. Some of these are antimetabolic Cadmium is especially *high and accumulates with age. Can an abnormal* trace metal affect a pyridoxal enzyme system so as to cause a conditioned local deficiency? If so, lipid metabolism might be altered.[98a]

William Dock points out in a personal communication:

> The reason why saturated fats are so important is becoming plain. Endogenous plasma cholesterol is largely esterified with unsaturated fatty acids, *the cholesterol* in atheromas, as MacArthur pointed out in 1942, is largely esterified with the commonest saturated fatty acid, palmitic acid The bile of normal people on low fat diet provides 1.5 Gm. of cholesterol a day On fatty diets, and in those with hypercholesterolemia, this may rise to 3 Gm or more In any event, about 70 per cent of the bile entering the duodenum, in food or bile, is reabsorbed. If this absorbed cholesterol is esterified with fats with iodine numbers around 125 (that of corn oil), the blood cholesterol does not rise appreciably. If esterified with fats with iodine numbers under 90, there is significant rise Since butter and beef fat have numbers under 40, and coconut oil has an iodine value of 7, 100 Gm. a day of these may double the β-globulin-bound cholesterol in the blood of a healthy young subject, and provides the inert ester found in the atheromas Ten eggs a day only double or triple the cholesterol available for alimentary absorption, but changing from 100 Gm of unheated fish or corn oil to 100 Gm. of fat from fried eggs may cause a ten- to twenty-fold increase in available saturated fatty acids Since the dairy products and eggs, so abundant in the diet of those prone to coronary disease contain both cholesterol and saturated fats it is not remarkable that it has taken 50 years to clarify the significance of the atherosclerosis which the Russians evoked in rabbits by feeding animal fat or pure cholesterol.

On the basis of all this evidence, I have been permitting my patients to take vegetable fat (mostly in the form of corn oil or another oil) up to their caloric requirements but [illegible] been reducing the animal fat intake [illegible] tically checking the blood lipid levels [illegible] detection of those in need of more [illegible]

reduction. Response to this regimen varies with the individual, much as it does to insulin or other drugs or to obesity diets In some patients, moderate restriction of animal fat results in a marked decrease in blood lipids, especially cholesterol, in many more, fat restriction for a long time is necessary to effect such a reduction. It is probable that the essential fatty acid content of fats in the diet should be at least 5 per cent if the serum cholesterol is to be kept down

Schroeder has proposed a somewhat similar regimen.[85a] He reduces the intake of saturated fat by about 50 per cent and provides 0 5 Gm. linolenate each day by use of soybean oil in salad dressing, sauces, and cooking In addition, he gives 5 to 10 mg of pyridoxine and 1 0 Gm of the calcium complex of ethylenediamine tetra-acetate.

Dietary protein may be as important as dietary fat in the metabolic background of atherosclerosis [35] As a rule, the protein intake is directly correlated with the fat intake It has been established that the serum α_1-lipoprotein fraction definitely rises in protein depletion due to plasmaphoresis or to a protein-free diet, or in states of malnutrition and chronic wasting, states in which the incidence and severity of atheroma are decreased

SITOSTEROLS The sitosterols are the most common of the phytosterols, the plant sterols Results of investigations of these sterols may prove to be important in solving some of the problems listed here There are at least five varieties of sitosterols—α_1-, α_2-, α_3-, β-, and γ-sitosterol The last two are isomers and are closely related to cholesterol. Investigation at present is concerned with β-sitosterol, and it is this substance which is referred to hereafter as sitosterol. β-Sitosterol, the principal sterol of cottonseed oil, tall oil, and wheat germ oil, is poorly absorbed by the body, γ-sitosterol is the principal sterol of soybean oil, it does not have the same effect as β-setosterol [12]

Chicks on an atherogenic, high-cholesterol, high-fat diet, when given sitosterol, had lower blood cholesterol levels and considerably less atheroma formation [84] Patients on their usual diets with supplementary crude soy bean sterol showed lowered cholesterol levels.[29] Sitosterol, in the form of a liquid (30 ml. contained 98 per cent pure sterol) was given in doses of 5 to 6 Gm immediately before meals to 14 subjects, 12 of them hypercholesterolemic, for 22 weeks, with periods of placebo control; in all of them the total serum cholesterol was decreased, the effect becoming evident at the end of the first week, with further declines subsequently.[12] No tendency to "escape" was noted for periods up to 18 weeks Neutral fats and the Sf 10 to 30 and 30 to 100 lipoproteins also decreased No decrease in phospholipids occurred

Best and associates[12] point out that the blood cholesterol level is apparently regulated by an efficient homeostatic mechanism, a fairly constant level being maintained in dynamic equilibrium The average life span (regeneration time) of a molecule of plasma cholesterol is about 12 days, cholesterol is therefore being continuously metabolized or excreted and replaced by synthesis or absorption from the intestinal tract The absorbed cholesterol includes that in the food and that excreted by the liver in the bile; since both are in the form of free rather than of esterified cholesterol, it is assumed that their absorption in the intestinal tract is the same The effect is therefore more efficacious than a mere restriction of dietary cholesterol.

It has been suggested that endogenous cholesterol synthesis varies inversely with the supply of dietary cholesterol.[35] The constant, suppressive effect of sitosterol over long periods of time supports the hypothesis that this substance blocks the reabsorption of endogenous cholesterol excreted in the bile, as well as the absorption of ingested cholesterol. It has been suggested that stimulating the excretion of bile, making more endogenous cholesterol available to the blocking action of sitosterol, potentiates hypocholesteremic action of the latter [19a]

By what mechanism sitosterol interferes with cholesterol absorption is not clear. The mixture of sterols, it has been suggested, causes formation of nonresorbable crystals.[88, 89] Another suggestion, based on findings in rats, is that the plant sterol interferes with the esterification of cholesterol, and hence with its absorption [42] Whatever the mechanism may be, the sitosterol should be taken as close to the meal as possible, to assure complete admixture. No adverse reactions have been reported The substance may be given in the liquid form, or as a biscuit.[9]

The fall in serum cholesterol with sitosterol administration is confirmed in other studies.[61] Sitosterol was given in the form of biscuits at each of the 3 meals; larger dosages (15 to 25 Gm. daily) seemed to be more effective.[9] Plasma cholesterol reductions of 10 to 14 per cent were noted in 6 of 10 patients given sitosterols.[103] My own experience, and that of others not yet reported, seems to indicate that the effect of sitosterol is irregular Significant falls in blood cholesterol occur in about two thirds of the patients who take sitosterol, but there is no way of predicting what the response will be. Investigators have noted that success with sitosterol occurs principally in patients in a "hypercholesterolemic state," which is not a disease entity but a mixed group with varying characteristics, furthermore, "sitosterols" are far from being of uniform composition, so that there are at least two variables so far.[63]

Electrophoretic studies have revealed that the β-lipoproteins decrease after sitosterol administration [49] Combined with the observation on its effect on the Sf particles, it would appear that sitosterol reduces not only the total cholesterol but also the lipid fractions usually incriminated in causing atheroma

With dosages of 7 Gm. of sitosterol daily, the blood cholesterol did not decrease [90] Sitosterols were found not to have an effect on intestinal absorption of cholesterol in man or rats, and caused no changes in the plasma cholesterol of 6 patients after 6 months of treatment.[27]

Should sitosterol fulfill its early promise, some patients with coronary disease will find life more bearable Use of sitosterol three times a day will then be indicated for patients who cannot or will not maintain a diet which will lower the blood lipids For the majority of patients, who follow the prescribed diet by and large, sitosterol for one meal a day or for the occasional splurge will mean a great deal At the moment, the evidence points to only very restrained optimism with regard to the use of this sterol in treatment

OTHER FACTORS

Factors inherent in the individual may modify or nullify the dietary efforts to control the blood lipids

Obesity seems not to be associated with hypercholesterolemia[55] or an excess of Sf 12 to 20 particles.[22] The population studies by Keys and co-workers[53] (*see* Chapter 3) disclose that in groups with a generally low level of blood cholesterol there is some correlation between the cholesterol concentration and relative obesity, but that in groups characterized by high serum cholesterol levels there is little relation between these levels and obesity. The overweight are generally conceded to manifest more pronounced fluctuations in cholesterol values than persons of normal weight. The blood cholesterol in the overweight decreases with dietary restriction, in those of normal weight it does not [53, 83]

The fiber content of the ingested food may have some bearing on the problem of diet and cholesterol values.[112] Diets low in fat are high in residue and contain large amounts of crude fiber. The cycle of intestinal absorption and excretion of cholesterol in the intestinal tract may be related in some way to this fact

The role of weight changes and caloric intake has not yet been determined exactly. A study of 24 women on diets containing approximately 1400 calories and 50 to 80 Gm of fat, who lost 15 to 60 pounds at rates of 0.6 to 2 pounds a week, and of 12 women who remained on free diets and lost no weight, disclosed that weight loss was unaccompanied by a decrease in blood levels of cholesterol or other lipids, if anything, these blood constituents seemed to increase slightly [75] Caloric intake as such has little influence on the blood lipids, any noticeable effect may be secondary to altered fat metabolism commonly associated with changes in caloric intake [53]

In contrast are the findings in 3 healthy young men on measured diets containing 150 to 175 Gm. of fat but varying in other constituents, doubling the caloric intake did not affect the serum lipids when the weight was kept down by exercise, with activities restricted and weight gain permitted, the cholesterol increased sharply and the β-lipoproteins increased in 2 of the 3 subjects, with weight loss due to restricted caloric intake, the high serum lipids promptly fell to their former levels [83] In my patients, I have almost never seen a decrease in serum cholesterol, whatever the regimen, when the patient was gaining weight Observations that weight loss, regardless of the subject's nutritional state at

the start, was associated with decreased levels of all three classes of Sf lipoproteins and of total cholesterol, and that weight gain, despite low dietary fat, was accompanied by an increase in these constituents, confirm the above findings.[113] Walker[113] concludes "If elevated serum lipid levels contribute to the causation of atherosclerosis, weight reduction is a proper treatment for this disease."

In general, it seems a little easier to bring down an abnormally high blood cholesterol level than to effect a decrease in a normal level, but the difference is not striking The variation in the individual's response to dietary measures presents greater difficulties

Although it now seems possible that drastic reduction of dietary fat will lower the blood cholesterol, the procedure may be dangerous In animals, such reduction, with carbohydrates substituted to make up the necessary calories, leads to fatty degeneration of liver and kidneys This may be due to a lack of essential unsaturated fatty acids Rats on a diet in which fat supplies less than 10 per cent of the calories soon show "changes in composition of body lipid suggestive of ageing "[92] Dogs need at least 16 per cent of their calories as fat and more than 1 per cent as unsaturated fatty acids in order to survive [92]

The minimal fat requirements of man have not been established. The scant observations on persons who have been completely deprived of fat for long periods seem to indicate that fatty acids are a dietary essential [18, 117] Some workers have suggested that such a deficiency may occur in patients treated with Kempner's rice diet,[114] but others found no evidence of significant liver damage after long periods of this diet [40]

When Page[92] cut his own fat consumption drastically he suffered from gastrointestinal disturbances, depression, and irritability. Weakness, gastric disturbance, constriction in the chest, or sense of impending collapse have been reported in some patients on low fat diets [92] On the other hand, patients on the practically fat-free rice and fruit diet for many months, whom I followed closely, seemed to suffer no ill effects, after an initial, usually considerable loss, the weight stabilized, and aside from grumbling about the diet the patients had few complaints. Others, too, have found that patients on this diet manifest few symptoms which can be directly charged to the diet.

Evidently, therefore, the basic human need for fat is not known. It is probably advisable not to reduce the daily fat quota below the point at which it provides less than 15 per cent of the daily caloric requirements. In any case, patients on low-fat diets should be given supplementary fat-soluble vitamins

Can excessive consumption of fat, especially cholesterol, cause or increase atheroma formation? This is not, as some believe, the obverse of the question whether low-fat diets will prevent atheroma formation or cause it to regress, for the basic implications of the problem are quite different.

Feeding unusual quantities of cholesterol to some animals, e g , rabbits, quickly causes coronary atheroma Other animals, e g , dogs, are more resistant, and additional traumatic means must be used. In still others, atheromatosis cannot be induced by dietary means. The differing behavior of the various animal species is reported in detail by Katz and Stammler [49]

So far as man is concerned, some investigators report that excessive ingestion of cholesterol does not raise its level in the serum [56, 76] Others have reported the contrary, thus, all the serum lipids increased in 1 subject fed fatty pemmican for 6 days,[93] the serum cholesterol increased in subjects on a meat and fat diet exclusively,[109] the blood cholesterol rose significantly after ingestion of large quantities of egg yolk powder [70]

While most of the observations on the effect of fat ingestion on human blood have been made on normal subjects, a more pertinent question is what happens when large quantities of animal fat are ingested by a patient with coronary disease Such subjects have already performed the "experiment of nature" and have conclusively demonstrated that their coronary arteries cannot satisfactorily handle the lipids presented to them

In an investigation of mine, reported in detail elsewhere,[87] three groups of 27 patients each were closely studied. All the members of the three groups were middle-aged men. Group A consisted of patients with known coronary disease (previous infarction or un-

equivocal angina pectoris). Group B comprised patients with coronary disease, matched as closely as possible for severity and stage of illness with Group A. Group C consisted of patients without evidence of cardiac disease and with normal electrocardiograms; all had duodenal ulcers and were on a high-cream, high-fat diet comparable in every respect to the diet of Group A. Groups B and C were taken from outpatient files, their records being matched as far as possible, with regard to age, height, weight, and occupation, to those of Group A.

A year or more after the diagnosis of coronary disease was made in Group A, peptic ulcer developed in every case; there were typical symptoms, and the diagnosis was confirmed by roentgenography. All the patients, on their own initiative or as directed by the physician, went on a high-milk, high-cream diet, in most cases the Sippy diet or some modification of it. Within 7 months after the start of this diet, 10 patients, all between the ages of 38 and 55, had died. In all 10 cases, circumstantial evidence pointed to cardiac infarction as the cause of death, in 6 of them this could be confirmed by postmortem examination. Advanced atheromatosis of one or more main coronary arteries was found in all 6 cases, and fresh thrombus was present in 4. Of the remaining 17 patients, none died within 1 year, but in 12 of them symptoms of angina pectoris appeared or grew worse within 3 months of starting the diet, in 14, the cardiac condition grew worse during the first year, and 7 had new infarctions. These figures, to my mind, strongly suggest that a high-animal-fat diet is harmful to persons with coronary disease. My subsequent observations on this type of patient have confirmed these figures.

In Group B, the condition of 9 patients deteriorated during the year of observation, 5 suffered infarctions, and 3 of them died.

In Group C, subjective or objective signs of heart disease developed in only 1 of the 27 patients during the year of observation, this patient had mild angina pectoris, but there were no changes in the electrocardiogram. It cannot be concluded from this that damage may not have started, or that continuing the high-fat diet in this age group might not eventually have resulted in vascular lesions.

A summary of the data obtained in this study is given in Table 5. From the observations just described, and substantiated by data on a larger series (still unpublished), I am led to conclude, at least as a working hypothesis, that (*1*) High-animal-fat (cream) diets seem to cause deterioration in the clinical course of coronary disease. (*2*) Similar diets cause no obvious cardiac changes, in a 1 year period, in men of the same age whose hearts are normal.

TABLE 5. EFFECT OF DIET ON THREE GROUPS (27 MIDDLE-AGED MEN IN EACH GROUP) WITH VARIOUS CONDITIONS

	Effects		
Group	*Death in 1 year*	*Infarction*	*Cardiac deterioration*
A coronary disease, duodenal ulcer, high-cream diet	10	22	24
B coronary disease, usual diet	3	5	9
C normal heart, duodenal ulcer, high-fat diet	0	0	1

In 6 of 14 patients with coronary disease, angina pectoris developed, not immediately but 3 to 5 hours after, the ingestion of a fat meal.[55] This period coincides with the height of postprandial lipemia. I have so far been unable to detect similar changes in my patients.

There is strong evidence that fat ingestion may increase the risk of increased blood clotting. The lipids may play an important role in *in vitro* blood coagulation, but it has not yet been established that they do so *in vivo* when the platelets are normal, nor is the mechanism clear.[78]

BLOOD LIPIDS, HORMONES, AND ATHEROMA FORMATION

The suspicion that the endocrine glands, especially the gonads, are in some way related to the pathogenesis of atheroma is ines-

capable Some aspects of this problem, as they relate to sex differences in coronary disease, were discussed in Chapter 2. Here the possibility that the glands' effect on the blood vessels may be mediated by changes in the blood lipids will be examined

Experimental studies have furnished the bulk of the available evidence. The conclusions drawn from such evidence obviously cannot be applied without further ado to other species of animals or to man, but they are nevertheless suggestive The review by Katz and Stammler[19] is comprehensive and supplies an indespensable bibliography.

GONADAL HORMONES

In animals, lipid metabolism and atherogenesis are affected by administration of thyroid hormone or adrenocortical steroids and by disturbances in pancreatic function, but in no clear-cut or conclusive fashion. The effect of gonadal hormones is much more definite, however. Coronary and aortic atherosclerosis ordinarily develop in cholesterol-fed cockerels, but concomitant administration of estrogens prevents atheroma formation The fact that aortic atherosclerosis continues to develop points up the observation that antherosclerosis advances at varying rates, presumably in response to differing conditions in different parts of the vascular bed During the hen's egg-producing season, when there is endogenous estrogen, diet-induced coronary artery disease is also prevented Estrogen has a prophylactic action even in depancreatized chicks or in those with hyperadrenalism and steroid diabetes induced by ACTH or corticoids In addition, estrogen prevents the hypertension usually induced by cortisone or DCA This is of some interest, since hypertension apparently accentuates atherogenesis in animals with experimental disturbances of lipid metabolism

Concurrently with preventing coronary atheroma, the estrogens exercise an effect (probably a necessary intermediate action) on the plasma lipids The phospholipids are increased, so that the plasma cholesterol–phospholipid ratio shifts toward normal There is a simultaneous shift in the α-lipoprotein–β-lipoprotein ratio and in the ultracentrifugal spectrum of the plasma lipoproteins. In each case, the change is in a direction *away from that currently thought to be atherogenic.*

The estrogens seems to be effective in therapy as well as in prevention. Administration of estrogens seems to have a beneficial effect on both the lipophage and the fibroblastic elements of coronary atheroma in cholesterol-fed chicks with advanced coronary lesions, despite continued cholesterol feeding The coronary arteries of chicks sacrificed within a few weeks after starting estrogen therapy showed almost no lesions. It seems clear, therefore, that coronary atheroma is a reversible process in this species.

In cockerels, estrogens have the same antiatheroma action even when androgens are given at the same time; however, the feminizing effect of the estrogens is prevented. Unfortunately, this effect is not duplicated in man

In rabbits, neither exogenous hormones nor endogenous ovarian secretion seem to have any suppresive influence on cholesterol-induced coronary atheroma [72, 73]

The cholesterol and phospholipid concentrations are normally about the same in male and female dogs But when atherosclerosis is induced by thiouracil and cholesterol administration, the phospholipid and cholesterol concentrations, as well as the cholesterol–phospholipid ratio, rise to higher levels in the male than in the female; this more precipitous rise starts soon after the start of the experiment.[10]

EVIDENCE IN MAN The concept that estrogen influences the blood lipids in man is receiving increasing support from accumulating evidence

Normally, the α-lipoprotein–β-lipoprotein ratio is relatively greater in young women than in young men of the same age.[97] Increasing concentrations of α_1-lipoprotein have been reported in postmenopausal women [64]

Administration of estrogens, whether ethynyl estradiol (Estinyl), estrone sulfate (Premarin), estradiol benzoate, or diethylstilbestrol, to postinfarctive patients produced a startling result: the cholesterol in the α-lipoprotein fraction increased and that in the β-lipoprotein fraction dropped.[95] The cholesterol–phospholipid ratio of the whole

plasma and in the β-lipoprotein fraction fell. In most instances, the plasma cholesterol level also decreased. The previously disturbed lipid values finally approached those of healthy young men After a cumulative effect for several weeks, a plateau is reached, but when estrogen is discontinued the lipids promptly return to pretreatment levels In another series of patients, ethynyl estradiol, 0 25 to 1 mg. daily by mouth, resulted in a significant fall in the cholesterol-phospholipid ratio, in half of the cases this change was due to a lowering of the serum cholesterol, in the remainder to increased phospholipid levels.[106] In 20 hypercholesterolemic men with coronary disease, ethynyl estradiol in doses of 0 2 to 0 6 mg. daily caused a 25 per cent decrease in the mean plasma cholesterol level (almost entirely cholesterol esters), the plasma phospholipids remained constant so that the abnormally high cholesterol-phospholipid ratio dropped to normal[79]

In a study of the relationship between the gonadal steroids and atherosclerosis in 16 subjects,[28] it was found that: (*1*) Hypogonadism in either sex, other endocrine functions remaining intact, is associated with a high α_1-lipoprotein concentration. (*2*) Estrogens increase these lipoproteins; normal thyroid function, however, may be a prerequisite (*3*)Androgens, including methyltestosterone, reduce α_1-lipoprotein concentrations. (*4*) Increased α_1-lipoprotein concentrations are often associated with lower levels of α_r-lipoprotein, and vice versa (*5*) Results of electrophoresis suggest that steroid-induced changes in lipoprotein levels are due to changes in the lipid fraction rather than in the protein moiety.

Estrone sulfate, 5 mg by mouth daily for 2 to 25 weeks, caused a sharp decrease in the cholesterol and total lipid levels in almost all of 17 men[80] The greatest reduction occurred between the second and tenth weeks, with continued therapy, however, the blood levels returned to pretreatment levels In patients with coronary disease, the serum β-lipoproteins and the Sf 12 to 100 particles fell when estrone sulfate was administered, 0 05 mg per kilogram of body weight, intravenously[51] In the normal male, diethylstilbestrol was found to increase the serum level of α_1-lipoprotein[28] Whereas premenopausal women are relatively exempt from coronary disease, women who have undergone surgical castration do not enjoy the same immunity.[91, 122]

Some investigators have found improvement in both symptoms and electrocardiographic pattern in patients with coronary disease treated with estrogens[31] Decreased coronary atheroma has been reported in patients treated with large dosages of estrogen (men for prostatic cancer, women for breast cancer).[94] No change in the incidence of chest pain or in the electrocardiogram was found in one series of patients with coronary disease given ethynyl estradiol[106] Results up to September, 1954, in a long-term investigation of this phase of their work, were reported by Katz and co-workers to be promising[60]

Effective dosages of estrogens invariably produce undesirable side reactions—gynecomastia, loss of libido, suppression of spermatogenesis, atrophy of tubular and Leydig cells; irritability, depression, and a tendency to salt and water retention (most undesirable in heart failure) may occur.[95, 99]

For many years, testosterone was given to patients with coronary disease for no better reason than that it had a nonspecific "tonic effect." It now appears, on the basis of a number of reports, that the androgens may have an undesirable effect in coronary disease In hypogonadal men, methyltestosterone considerably reduces the serum concentration of α_1-lipoprotein, and this effect is not prevented by estrogens[29] Methyltestosterone was found to decrease consistently the total cholesterol in the α-lipoproteins. Small doses of methyltestosterone neutralized the apparently beneficial effect of estrogens on the blood lipids, in marked contrast to the findings in chicks Androgens therefore cannot be given in the expectation that they will merely neutralize the feminizing effects of estrogens without adversely affecting the lipid metabolism Androgens have been found to render the lipoprotein pattern of the eunuch, the eunuchoid, the normal male, and the normally immune premenopausal female "more atherogenic", the suggestion is made that the estrogens accomplish their beneficial action by depressing androgen production via suppression of pituitary gonadotropin or by neutralizing circulating androgens[20]

The demonstrated action of sex hormones on the blood lipids is of great theoretic and practical importance. Since these blood constituents are shown to be subject to hormonal control, both the causes of coronary disease and the therapeutic implications need careful consideration.

THYROID GLAND AND LIPID METABOLISM

It is usually accepted that hypothyroidism (myxedema) increases the tendency to coronary disease;[57, 100] this takes the form of *classic atheroma, and probably is related to* the increase in blood lipids. The fact that the blood cholesterol is high in myxedema has been known for a long time;[83] more recently, it has been established that the mean total lipid, total cholesterol, phospholipids, and β-lipoprotein are all increased while the α-lipoproteins change only slightly.[47, 61] These deviations from normal are qualitatively the same as those found in idiopathic hypercholesterolemia, a condition in which coronary disease is frequent; in myxedema, however, the rise in β-lipoprotein is not as great.[47] It is therefore possible that different mechanisms are responsible for the blood lipid changes in the two conditions. The administration of sitosterols reportedly induces a reduction of all the blood lipids in myxedema.[13]

OTHER DISORDERS OF LIPID METABOLISM

Diabetes mellitus, myxedema, and the nephrotic stage of chronic glomerulonephritis are characterized by high blood levels of cholesterol and a high incidence of coronary disease. There is also a heterogeneous group of disorders characterized by disturbances of lipid metabolism, associated in some cases with skin deposits of lipids and/or atheroma.[11, 62, 108, 120]

For the metabolic disorder in which there is a characteristic increase of the total blood cholesterol, a normal proportion of cholesterol esters, and an increase in phospholipids, Wilkinson[120] prefers the term "essential familial hypercholesterolemia." Life expectancy for the heterozygous individual with this abnormality is normal; in the homozygous individual, however, atheroma may develop at an early age. Xanthoma tuberosum is the form of the disorder in the homozygous. The blood cholesterol level is not influenced by dietary measures, lipotropic substances, or thyroid extract.

Cogent arguments are advanced by Adlersberg[1] *for the concept that hypercholesterolemia*, atheroma (especially in persons before age 50), and xanthomatosis are different aspects of an inborn error of metabolism with *important genetic factors. In the majority of* his patients with coronary disease below the age of 50, the serum cholesterol levels were high; one third to one half of their siblings *also had high blood cholesterol levels*, and many had arcus senilis and xanthelasma; a few had xanthoma. Genetic analysis revealed that these individuals fitted into a 1:1 mendelian ratio, and the metabolic defect was probably transmitted as a dominant trait. He suggests that the heterozygotes are those with uncomplicated coronary disease who carry one gene responsible for faulty lipid metabolism; the homozygotes are the ones who carry two genes and have familial xanthomatosis. Wheeler,[115] too, concludes that hypercholesterolemic xanthomatosis is an inherited disorder transmitted by simple mendelian dominance.

In essential or idiopathic hyperlipemia, which is usually held to be a benign disease, the serum contains large quantities of neutral fat and turns milky on standing. As a rule, the serum concentration of the phospholipids and cholesterol, both free and esterified, is increased. The condition is not without danger: of 7 patients with an average age of 46, 4 showed definite evidence of premature atherosclerosis.[101] Others are of the same opinion, and propose that xanthomas of the extensor tendons of the fingers, tuberous xanthoma, and coronary disease occur quite frequently in both idiopathic hyperlipemia and primary hypercholesterolemic xanthomatosis[62] (Figs. 21 and 22). Table 6 gives the differential diagnostic features of the two conditions.

Three types of xanthomatous skin lesions may occur in coronary disease: xanthelasma, xanthoma tuberosum, and xanthoma diabeticorum.



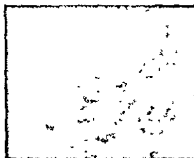
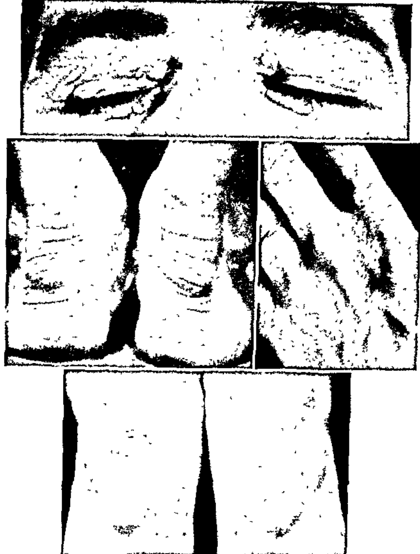




FIG 21 Idiopathic hyperlipemia (Top) Tuberous xanthomas on hands (Middle) Eruptive xanthomas on buttocks and knee (Bottom) Tuberous xanthomas on elbows (From Lever et al[illegible])



:2 Primary hypercholesterolemic xanthomatosis nthelasmas of eyelids (Middle left) Xanthomas ʼes tendons (Middle right) Tendon xanthoma distal to knuckle of middle finger (Bottom) Xanthomas of patellar tendons (From Lever et al[62])

ELASMA

known as xanthelasma palpebrarum, lly appears in the fifth or sixth decade and occasionally earlier The lesion s of a soft, yellowish plaque which in- the eyelid and especially the inner s Coronary disease, hypertension, or s is present in at least one third of the s with this lesion

blood cholesterol level is increased in cent, and in 20 per cent or more of s advanced coronary disease is pres- No definite pattern of Sf particles has found. Thannhauser[108] concludes that ion is "always a symptom of familial hypercholesterolemic xanthomatosis," and coronary involvement may be found in about 50 per cent of the patients. Elevated levels of blood lipids are said to occur in 50 per cent of cases of xanthoma of the eyelids alone, in half of these (25 per cent of total) there is evidence of cardiovascular disease[74] This coincides closely with my own experience In any event, all patients with xanthelasma *should be carefully followed.*

XANTHOMA TUBEROSUM

This lesion may appear at any age, but is most common in young adults, developing at a much earlier age in males than in females.

TABLE 6. DIFFERENTIAL DIAGNOSTIC FEATURES OF FAMILIAL HYPERCHOLESTEROLEMIC XANTHOMATOSIS AND IDIOPATHIC HYPERLIPEMIA

Diagnostic feature	*Xanthomatosis*	*Lipemia*
Serum	Clear	Turbid
Cholesterol level	Increased	Increased
Phospholipid level	Increased	Increased
Neutral fat level	Normal	Increased
Electrophoretic pattern	β_1-Lipoprotein always increased	α_2-, or $\alpha_2+\beta_1$-Lipoprotein elevated
Chemical protein fractionation	α_1-Lipoprotein normal, β_1-Lipoprotein greatly increased	α_1-Lipoprotein normal, β_1-Lipoprotein greatly increased
Glycoproteins	α_1-, α_2-Lipoproteins normal, β-lipoprotein moderately increased	α_1-, α_2-Lipoprotein normal, β-Lipoprotein moderately elevated
Sedimentation rate	Increased	Increased
Xanthomas		
Papular	Absent	Common
Tuberous	Common	Common
Eyelids	Common	Absent
Achilles tendon	Common	Absent
Patella	Common	Absent
Extensor tendons of fingers	Present	Present
Hepatosplenomegaly	Absent	Common
Abdominal cramps	Absent	Possible
Coronary disease	Common	Common

The sites of predilection for the yellow to brown papules, nodules, or plaques (sometimes tumors) are on the extensor surfaces around the large joints, especially the elbows, knees, hips, and heels The axillas, palms, soles, tendon sheaths, and synovial membranes may occasionally be affected The coronary arteries are involved in 40 to 50 per cent of the cases. Hypercholesterolemia is extremely common and may be severe. The Sf 20 to 100 lipoproteins are considerably increased [34]

XANTHOMA DIABETICORUM

Another name for this condition is xanthoma eruptivum. The lesion resembles xanthoma tuberosum, but is of smaller size and occurs in greater numbers Diabetes mellitus is the condition in which it occurs most frequently, and there is usually an associated hypercholesterolemia

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CHAPTER 5

Tobacco

THERE is no longer much doubt that smoking affects the circulatory apparatus, although the effect in some individuals is much greater than in others. That smoking aggravates existing disease also seems probable, but whether it can induce disease in healthy tissue is a matter of controversy

In normal man, the cardiovascular changes that occur with smoking are. (*1*) increase in heart rate, (*2*) increase in systolic and diastolic blood pressure, (*3*) cutaneous vasoconstriction,[13] (*4*) occasional ectopic contractions, and (*5*) occasional electrocardiographic and ballistocardiographic changes

Nicotine is probably responsible for the changes in the circulatory system produced by smoking Cigarets made of cornsilk or of a practically nicotine-free tobacco do not cause these changes Smoking of denicotinized or of filter-type cigarets produces ballistocardiographic changes, although in one study it was found that the ballistocardiogram is less sensitive to the denicotinized cigarets than to regular ones.[32] A cigaret with a nicotine content of 0.23 per cent (⅕ of a regular cigaret) may produce the same physiologic response as the intravenous administration of 0 6 mg. of nicotine alkaloid.[26] The changes after smoking a pipe or cigar, chewing tobacco, or taking snuff are less marked Nicotine given sublingually or parenterally will cause the same changes as smoking. The worst offenders, apparently, are the regular cigarets.

Pharmacologic investigation of the cardiac reactions to nicotine has given inconclusive results In a study of revived human heart, perfused under constant pressure according to the Langendorf method, a decrease in coronary flow and an increase in the rate of amplitude of ventricular contraction were noted[22] On rings of human coronary artery, nicotine has no effect or it constricts them In the whole animal, however, the effect of nicotine closely resembles that of epinephrine, *causing an increase in blood* pressure and in coronary flow In the isolated rabbit heart, small amounts of nicotine increased the coronary flow, in toxic doses it reduced the flow[23] Smoking has been reported to raise the blood sugar,[2] but the effect is inconstant.[1] In heart-lung preparations in the anesthetized dog, nicotine at first increases the coronary blood flow, this is followed by a prolonged reduction in flow resembling in rate of onset and duration that produced by pituitary extract.[4]

MECHANISM OF ACTION

Nicotine does not act, as some have suggested, by stimulating the adrenal glands In sympathectomized animals, nicotine has no effect on the blood flow, indicating that epinephrine probably does not mediate its effect.[30] The fact that intravenous administration of small amounts of nicotine induced circulatory effects without concomitant hyperglycemia was a further indication that adrenal secretions do not play a role in the action of nicotine The speed of the ballistocardiographic reaction to smoking makes it seem unlikely that the effect of nicotine is mediated via the pituitary gland[7]

Whether or not nicotine impairs the coronary circulation is still uncertain. According to some, coronary spasm is possible, and does occasionally occur in smoking; atropine given before smoking prevented electrocardiographic changes.[2, 18, 37] Bryant and Wood[3] concluded that in exceptional cases smoking

can cause angina pectoris not induced by exertion, and that this symptom and the electrocardiographic changes are the result of coronary spasm But the failure of nitroglycerin to abolish the electrocardiographic changes induced by nicotine has been cited as evidence that coronary spasm is not a factor in producing these changes [32]

Results of experimental studies in animals strongly suggest that nicotine stimulates the hypothalamic-pituitary axis. This releases vasopressin,[5] which in turn constricts the coronary arteries in animals,[4] and possibly in man.[31] Some suggest that this is the mechanism by which smoking might cause a reduction in coronary blood flow,[6] there is no direct evidence, however, that this mechanism operates in man Low-grade exposure to carbon monoxide and allergy to tobacco have also been proposed as possible causative factors [33]

Others, on the other hand, are of the opinion that increased heart work, as shown by the rise in blood pressure and in heart rate, can lead to myocardial ischemia [14, 29] Still others hold that the ballistocardiographic changes are not due to cardiac ischemia, since changes in the electrocardiogram or anginal pain are seldom encountered in subjects with ballistocardiographic changes after smoking; coronary vasoconstriction (except possibly in collateral vessels) would therefore seem unlikely [7] The last-mentioned believe that nicotine acts principally by its direct effect on the myocardium, although coronary and peripheral arteriolar constriction or pooling of blood in splanchnic veins may play a role

The rare but undoubted occurrence of angina pectoris and ischemic changes in the electrocardiogram lead me to believe that smoking probably can cause relative coronary insufficiency, which may be the result of a disturbed coronary flow, or, more likely, of an increased metabolic demand of the heart muscle Chest pain radiating to the left arm during smoking was a complaint of 3 of my patients 1 to 2 weeks preceding an acute infarction A similar case has been reported in the literature [20] Presumably, this occurred during a period of relative coronary insufficiency, which is so often premonitory of infarction.

EFFECT OF SMOKING

In a study[32] of 28 healthy subjects, the heart rate increased an average of 18 beats per minute in 25 after smoking 1 cigaret, the average increase in blood pressure in 16 of the 28 was 16 mm Hg systolic and 10 mm diastolic. Electrocardiographic changes other than tachycardia were found in 16, they consisted of decreased amplitude of T_1 and T_2 waves in 13, and of minor changes in the P–R interval or in the amplitude of the main complex in 3 cases Significant depression of the S–T segment and inversion of T waves in various leads was found in 2 subjects, both had persistent precordial pain and coronary disease had been diagnosed Administration of 1/150 gram of nitroglycerin before smoking did not prevent the appearance of electrocardiographic or ballistocardiographic changes after smoking in any of the subjects Since this confirms earlier work[13] showing that amyl nitrite does not prevent T wave changes induced by nicotine, it was concluded that coronary vasoconstriction did not cause the changes.

The most pronounced changes due to smoking are found in the presence of some degree of coronary involvement. In the absence of coronary involvement, the electrocardiogram is affected only slightly, and in a relatively small number of persons.[32] Ischemic changes in the electrocardiogram after smoking were first reported in 1939 in 2 patients with angina pectoris [37] Bryant and Wood[2] then summarized the literature and added 16 patients with angina in whom electrocardiograms were taken after smoking 2 cigarets Minor T wave deviations were found in 11, these, correctly in my opinion, were attributed to changes in heart rate and were considered within normal limits Unequivocal deterioration resembling that of cardiac ischemia was found in 2 cases.

In a study[1] of 46 subjects (18 normal, 24 with coronary disease, and 4 with peripheral vascular disease), 2 mg of nicotine bitartrate, corresponding to the amount of nicotine absorbed by inhaling cigaret smoke five times in 1 minute, was given by vein Some members of all three groups showed slight electrocardiographic changes, in 4 of the patients with coronary disease there were

major changes, and 2 of them who were suffering from spontaneous angina felt pain at the time the changes were noted on the electrocardiogram.

The ballistocardiogram is more sensitive to the effects of smoking than the electrocardiogram Changes in the ballistocardiogram were first noted by Levy and associates,[24, 25] who found an increase in heart rate and cardiac output Later, using high-frequency recording, Dock and co-workers[7] demonstrated variations which ranged from those which might be considered within normal limits (rise in rate and in I–J amplitude) to distinctly pathologic changes (J wave decrease during expiration, or striking changes in diastolic waves—decrease in J with tall L) In one study,[3] 400 normal subjects were tested after smoking 1 cigaret, abnormal tracings were found in 10 per cent—5 per cent of those under the age of 30 and 15 per cent in those between the ages of 30 and 40. The most typical change was a decrease in the size of the H, I, J, and K waves, with marked notching of the J wave A shallow I wave was the next most common finding. In another study,[17] ballistocardiographic changes were rarely produced in healthy subjects under the age of 40 who smoked 1 cigaret, and only occasionally in healthy subjects over the age of 40

In 40 patients with evidence of coronary disease, the ballistocardiogram became abnormal in 38 per cent after 1 cigaret.[17] In most patients with healed infarcts or with angina pectoris, smoking will cause further changes in an abnormal ballistocardiogram, or change a hitherto normal tracing into an abnormal one. It will do so much more regularly than either exercise or eating, this effect is the basis of a useful test in differential diagnosis (*see* Chapter 12) Even in a patient with clinical evidence of a completely healed infarct, only a few puffs on a cigaret may be sufficient to cause deterioration in the tracing. Occasionally, in a patient with angina pectoris, whose usual ballistocardiographic abnormality is diminished by exercise, smoking will produce marked changes in the ballistocardiogram In 1 such case, the electrocardiogram was normal even after a double Master test, in another case, the severest anginal pain occurred when the patient exercised after smoking.[7] In about half the cases, 1 or 2 ounces of whiskey improves the ballistocardiographic response to smoking; this is ascribed to the effect of the whiskey on the peripheral circulation rather than on the heart or coronary vessels[33]

Smoking is more likely to cause ballistocardiographic changes in persons who are without objective evidence of cardiovascular impairment but complain of dizziness, or palpitation, and in patients with thromboangiitis obliterans, Raynaud's disease, peptic ulcer, or hypertension.[7]

TOBACCO ANGINA

This entity was first named and described in 1899, by Huchard[18] It occurs for the most part in persons with typical angina pectoris in whom exercise or smoking induces attacks, or in whom smoking reduces the tolerance to exertion In another group, a smaller one, smoking is the only precipitant of anginal pain Abstinence from tobacco eliminates all attacks in some members of both groups In a third, extremely small group, definite angina occurs without other evidence of coronary disease. Some have interpreted this as an indication of vasoconstriction of the coronary arteries However, the ballistocardiogram has invariably been abnormal in such cases and the individuals affected were as a rule not younger than 25; it therefore seems much more likely that smoking induces true angina only in those whose coronary arteries are already somewhat narrowed Russek and co-workers,[32] who object to the term "tobacco angina" on the ground that the condition is not a true angina pectoris, define a clinical entity which they call "tobacco heart", this condition may be associated with precordial discomfort, ectopic beats, paroxysmal tachycardia, dyspnea, dizziness, and changes in the electrocardiogram or ballistocardiogram. All the symptoms and changes disappear when the patient stops smoking Clinical improvement was reported in 16 patients with angina pectoris who stopped smoking after a positive ballistocardiographic test; in 7, the chest pain disappeared completely[29]

STATISTICAL EVIDENCE OF EFFECT OF SMOKING

In 1938, Raymond Pearl[37] reported that the life expectancy of smokers was shorter than that of nonsmokers, the lessening increasing progressively with the amount of smoking At about the same time, a study of 100 men under the age of 40 with coronary disease disclosed that 93 per cent of 88 men in this age category were smokers[11] The incidence of coronary disease in patients under the age of 50 at the Mayo Clinic was greater among smokers than among nonsmokers; the same seemed to be true of the 50 to 59 year old group A recent report states that the relative incidence of coronary disease, especially in the younger age groups, was one and a half times greater in the smokers than in the nonsmokers[8] Coronary disease is reported to occur twice as often in smokers as in nonsmokers, the possibility that smoking may influence the intestinal absorption of fat and the chylomicron content of the serum is suggested[21] Another study indicates that coronary disease occurs earlier and that death occurs at an earlier stage among heavy smokers[31] The percentage of patients with coronary disease who are "excessive" smokers is variously given as 13 per cent,[19] 17 per cent,[24] 24 4 per cent,[36] and 50 per cent.[20] A Swiss study[16] which included 149 men over the age of 50, found that 6 7 per cent of those with coronary disease and 25 5 per cent in the control group were nonsmokers; 45 per cent of the patients and only 28.5 per cent of the control group smoked more than 20 cigarets a day, the younger the patient, the more likely it was that he would be a heavy smoker

Two recent studies[9, 15] provide the most impressive statistics on the role of tobacco in coronary disease The first was from Great Britain, the other from the United States. The British study[9] was primarily one on the mortality in the medical profession, 230 deaths were attributed to coronary disease. The mortality rate of those over the age of 35 rose from 3.9 per 1000 among the nonsmokers to 5 2 per 1000 among smokers of 25 Gm. or more of tobacco a day No data were given for the relative mortality rates of cigaret smokers as compared to consumers of other types of tobaccos because the latter group was very small

The investigation in the United States,[15] the most extensive so far, is a by-product of the interest of the American Cancer Society in pulmonary cancer. The smoking history of 190,134 men between the ages of 50 and 69 in various parts of the country was obtained in the first 5 months of 1952. Follow-up studies on 187,766 (99 8 per cent of the total) were obtained after 18 months A total of 4854 (2.6 per cent) had died, and details of the certified cause of death were available for 4710. The investigators were surprised to find an apparently definite relationship between coronary disease and cigaret smoking Since it seemed unlikely that the original survey included men who were already seriously ill, the deaths in this first period included a particularly high proportion due to acute disease, coronary disease accounted for almost half of the total number of deaths The coronary death rate was 95 per cent higher among regular cigaret smokers between the ages of 50 and 64 than among nonsmokers; it was 120 per cent higher among those smoking more than 20 cigarets a day at the time they were questioned. In the group between the years 65 and 69, the difference was only 15 per cent. No increased mortality could be discerned among cigar and pipe smokers.

An editorial in the *British Medical Journal*[35] on the results of the two studies just cited states:

> The agreement between these two investigations—the one large-scale, the other smaller but based on a more homogeneous population—makes it difficult to believe that the association is not real Whether it is causal can, in the long run, be most effectively proved by seeing whether abstention from cigarettes brings about a reduction in the mortality from the disease Some will doubtless prefer to believe that the habit of smoking and death from coronary disease are related only in that both are the product of a third and common cause. Occupation requiring only light physical work, which has been shown to be associated with coronary thrombosis, might, for example, provide greater opportunities for heavy cigarette smoking The association would, however, need to be very strong to account for those obtained among doctors

Another factor which might have been mentioned is that persons with the same kind of emotional and nervous tensions might be addicted to smoking and suffer from coronary disease. Still another possibility is that nicotine may disturb lipid metabolism in a direction harmful to the *coronary arteries.*[12, 19] *There is as yet no* convincing demonstration that nicotine damages the coronary vascular tisue If coronary vasospasm does indeed occur, it is conceivable that innumerable, repeated episodes could ultimately cause structural damage.

THERAPEUTIC AND PREVENTIVE IMPLICATIONS

Well publicized though all of the foregoing may be, the normal, healthy individual will no doubt pay little attention to it Most persons are skeptical about their positions on a graph But upon the physician devolves the duty of presenting these data to his patients, the following, in particular, must be warned that smoking is an added risk to the heart (*1*) patients with bad family histories, diabetes, obesity, or hypertension, all of whom are likely to be vulnerable, (*2*) patients with circulatory symptoms after smoking, *e g.*, tobacco angina or tobacco heart, (*3*) patients whose electrocardiogram or ballistocardiogram shows changes after smoking

In the case of established coronary disease, the problem is more serious and immediate Since all evidence points to the fact that nicotine can be harmful, I have for some time been advising complete abstention from smoking to all such patients Some cardiologists permit use of tobacco to patients with inactive heart disease if this gives emotional satisfaction and if, presumably, it does not induce angina For my part, I would rather not assume the responsibility of deciding that a patient will not suffer any ill effects. For the occasional patient who finds it "impossible to give it up," a change from cigaret smoking to pipe or cigar may be tried. But complete abstention is the only wise procedure if angina or electrocardiographic or ballistocardiographic changes occur with smoking.

SUMMARY

It has been definitely established that:

1. Smoking causes temporary disturbances in the vascular tree of some normal persons

2 Individual susceptibility to the cardiovascular effects of smoking varies widely.

3. The effects of cigaret smoking are much more marked than those of cigar or pipe smoking

4. In the presence of coronary disease, the vascular system reacts much more readily to smoking.

5. The effects of smoking are due to nicotine.

A number of questions not yet definitely answered are

1 Does nicotine cause spasm of the coronary arteries or does it act directly on the myocardium?

2 Does nicotine cause structural damage to the coronary arteries? Experimental proof is lacking, so far

3 What is the cause of the more common occurrence of coronary disease in smokers than in nonsmokers, as would seem to be borne out by statistical studies?

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CHAPTER 6

Pathology

KNOWLEDGE OF an organ's structure, its functions and their interrelations, and the changes wrought by disease, when integrated with clinical findings, forms the essential fabric of clinical medicine. The slow development of one or more strands of this fabric, or the inability to synthesize them has always hampered the physician. Nowhere in clinical science is the truth of this so evident as in the study of the coronary arteries, but in no other field was the integration carried out so successfully and so swiftly, once the fundamental threads were recognized Loose ends may still puzzle the clinician, but a clinicopathologic pattern has been so well defined that the many pains and confusion which attended the development of this pattern can scarcely be realized now

ANATOMIC CHANGES WITH AGE

Definite changes occur in the walls of the coronary arteries with advancing age.[15] The precise place for the shadowy dividing line between the changes of disease and those of normal aging is often difficult to discern, and in many cases morbid histologic changes seem to be those of accelerated senescence.

The earliest changes in the anterior descending coronary artery may be found at birth. The lamina elastica interna splits and a new elastic muscular layer forms between the inner limiting lamella and the lamina elastica A hyperplastic layer, composed of connective tissue on the inner side and hyperplastic elastic tissue on the outer, develops on the inner side of this muscular layer, and may be recognized during the first decade of life, the two components of the hyperplastic layer are at times difficult to distinguish. If the inner limiting lamella has undergone considerable splitting, its limits are not easily recognized and the inner portion of the intima is then called the diffuse layer. The changes in the various coronary arteries do not develop at a uniform rate For example, the lamina elastica interna in the posterior descending ramus may not split until the end of the first decade and the hyperplastic layer may not appear until the third In the anterior descending branch, beading may be detected in the first decade and calcification in the third, but in the posterior descending branch neither is normally found until the seventh decade

The coronary arteries undergo greater stress than other muscular arteries Proof of this is the common finding, even in early youth, of a buffering layer of fibrous tissue and smooth unstriped muscle in the subendothelial intimal layer, especially in the proximal portion of the left coronary artery Several factors account for the vulnerability of these arteries [42] (*1*) They originate at the aortic ring, where the arterial pressures are highest (*2*) During part of the cardiac cycle they are under a peculiar double strain, subjected on the one hand to the pressure of blood ejected from the aorta and on the other to the simultaneous resistance during systole resulting from compression of the intramyocardial branches by the contracting myocardium. (*3*) Two anatomic factors probably also play a role—the course of the left coronary artery, which originates almost at right angles to the aorta and then abruptly changes its path so that it runs parallel to the aortic wall; and the branching off of the large circumflex artery. The right coronary is somewhat less subject to excessive strain, so that it suffers less frequently, at least in the earlier decades of life, from

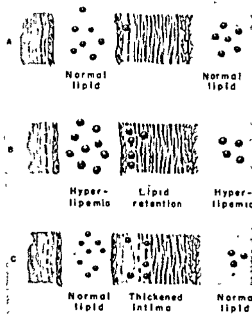


FIG 23 Schematic representation of filtration theory of atherogenesis A, normal plasma lipids, normal arterial wall, B, hyperlipemic plasma, normal arterial wall, greater lipid retention in arterial wall, C, normal plasma lipids, arterial wall with thickened intima and fragmented internal elastic lamina, lipids pass through arterial wall (From Page [57])

atherosclerosis In later life, lesions are found on both sides with almost equal frequency

INTIMAL LESION

It is now a widely accepted concept that the earliest atheromatous lesion of the coronary arteries in man is probably in the intima Although early changes in the arterial wall have been observed, most of our theories are based on the inferences drawn from older lesions in man or from animal experiments. The weakness of such reasoning is apparent, nevertheless, it provides the framework for what is at the very least a reasonable working hypothesis (Figs 23, 24).

Leary[42] formulated this theory as follows The early lesion of coronary atherosclerosis is intimal, and lesions of the media, and less often of the elastica, are secondary Four stages may be distinguished in youth: Lipidosis, phagocytosis, fibrosis, and necrosis. In the first stage, free lipid is deposited beneath the intimal endothelium and accumulates as fine granules in the intimal ground substance. In the second stage, phagocytes resembling fibroblasts pick up the lipid esters, forming the so-called foam cells, the esters are then split into finer droplets which eventually disappear The foam cells arise locally in the subendothelial connective tissue, and either migrate to deeper sites in the artery or, in progressive atherosclerosis, stimulate the growth of fibrous tissue. The fibrosis, which is the third stage, may be focal or, more often, diffuse, and consists of reticular strands between the cells which increase in thickness until the cells disappear. The lesion is apt to affect one side of the artery rather than run evenly around it, so that the resulting plaque is crescentic In the fourth, or necrotic, stage, the lipid cells accumulate

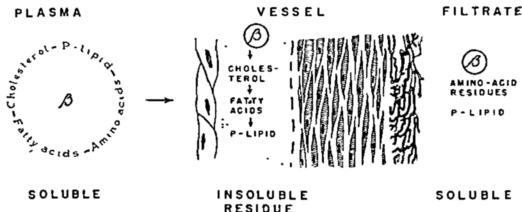


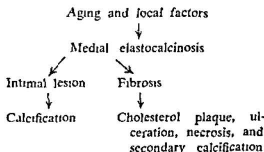
FIG 24 Schematic representation of passage of lipoproteins through arterial wall, lipid laden lipoprotein disrupted within the wall producing an insoluble residue which provokes tissue reaction (From Page [57])

without adequate supporting tissue and with poor vascularization, and the deeper layers, next to the media, become necrotic Lymphoid infiltration, previously absent, may now become conspicuous. In some cases, a focal fibrinoid necrosis, different in character from the slow nutritional necrosis, appears in the relatively well nourished fibrous tissue near the lumen and extends to the endothelial layer. This fibrinoid substance may represent organizing fibrin,[13] but more probably is partially necrotic collagen[75] Surface thrombosis sometimes follows this type of necrosis

A somewhat different reaction is found in older individuals, and occasionally in younger ones Fibrosis is minimal, but scarring persists from earlier lesions The new cells penetrate deeply, form large collections with eventual necrosis, and free the lipid, thus forming an "atheromatous abscess"[43] The cavity is filled with cholesterol crystals, some viable lipid cells, cell detritus, and a *fluid containing esterified or free lipid* The terminal process in the abscess may take a number of forms (*1*) Calcification may occur after liberation of glycerin and cholesterol, with formation of calcium soaps, this is a late, unimportant process. (*2*) Hemorrhage into the abscess is possible, either directly from the arterial lumen or from surrounding blood vessels (*3*) Finally, the abscess may rupture The consequences of such a rupture in the aorta may not be serious, since the contents are washed away. In the coronary arteries, however, the contents serve as a nucleus for a thrombus or they plug the lumen with a semisolid mass, *which may cause sudden death This sort* of "downstream" embolus must be rare, I have never seen an example of which I could be certain

The lamina interna elastica loses its integrity early, splitting into fragments and even disappearing Rarely, it is pushed ahead of the plaque. The media atrophies and thins out. The adventitia, too, shows changes Lymphocytic infiltration, sometimes perivascular and consisting in part of plasma cells, is often present Occasionally, this process is associated with newly formed vasa vasorum, so that the clinical picture may resemble that of syphilis.

Some investigators do not accept the theory that the earliest or primary lesion is in the intima. Thus, Crawford and Levene,[17] basing their opinion mainly on studies of the aorta and iliac arteries, have suggested that medial thinning beneath plaques, rather than being the result of pressure or of disuse atrophy, is an essential part of the atheromatous process, "comparable to a *shallow aneurysm partially or completely* filled by the plaque of intimal thickening." According to Bevans and associates,[4] the *early lesion in canine atherosclerosis* (induced by cholesterol and thiouracil) consists of lipid deposits in the media. The same is apparently true in chicks[62] Evidence presented by Lansing and associates[40] would seem to indicate that the primary pathologic process, which they termed elastocalcinosis, is a progressive increase, with age, in the *calcium content of the media, mainly in* or on the elastic fibers The sequence of events, as envisaged by them, is:



Such a concept has the advantage of explaining the dissociation between calcification and cholesterol deposition so commonly observed For example, deposits of lime are *found accompanied by minimal lipid infiltration*; heavy deposits of lipid are sometimes unaccompanied by intimal calcification; intimal fibrosis may occur without cholesterol *or calcium deposition in the intima.*

A small but important group of observers, led by Duguid,[20, 21] believes that atheroma starts with thrombus formation on the wall of the artery, the plaque being secondary. After the thrombus is laid down in the artery, it is covered with endothelium and incorporated into the arterial wall; once organized, it forms a fibrous thickening of the intima. Since the thrombi also undergo some fatty degeneration, a combination of lipid change and fibrosis results Not all atherosclerosis is of thrombotic origin, but they feel that

there is good reason for assuming that the atheromas which narrow the vessel started as thrombi.

According to Moon and Rinehart,[51] the earliest intimal lesion is a subendothelial proliferation of fibroblasts, with deposition of mucoid ground substance. They frequently found a fragmented lamina elastica interna, and phagocytized sudanophilic lipid material within globular macrophages in the intima Enos and associates report finding these processes in early lesions, and emphasize the factor of stress in determining the localization of atheroma

ARTERIOLAR LESION

The coronary arterioles are remarkably immune to pathologic changes, even in the presence of severe lesions in the main branches. Diseases notoriously associated with arteriolar lesions elsewhere in the body, such as malignant hypertension, cause few changes in coronary arterioles. Pathologic changes in the small vessels, when they occur, are seen most often in the substance of the left papillary muscles and under the epicardium, rather than in the myocardium The arteriolar lesions were studied in detail in a series of 71 cases, including a unique case of widespread infarction of the myocardium with normal main coronary arteries, the coronary arterioles in this case showed severe hyalinization, whereas elsewhere in the body the arterioles appeared normal[13] It is not known whether the patient had suffered from hypertension

This relative freedom of the coronary arterioles from pathologic changes should not lead to the conclusion that the smaller coronary vessels are unimportant in the causation of infarction On the contrary, as I have stressed elsewhere (*see* Chapter 1), changes in small arteries, arterioles, and even capillaries, especially if they represent collateral vessels, may be the determining factor in causing infarction

MECHANISM OF ISCHEMIA

Atheroma of the coronary arteries produces ischemia and infarction by a progressive narrowing of the arterial lumen or by a complete occlusion of the blood vessel.

PROGRESSIVE NARROWING

The course of an atheroma, once it has formed, may be divided into four stages, the entire process being variously known as atheromatosis, sclerosis, arteriosclerosis, or atherosclerosis. Stage 1 is asymptomatic; Stage 2 is one of cardiac symptoms, especially angina pectoris, Stage 3 is that of gradual infarction (fibrosis), and Stage 4 is acute infarction. The asymptomatic stage is always present early in atherosclerosis The second stage may be skipped en route to Stages 3 and 4, but often accompanies Stage 3. Acute infarction, the last stage, is seldom reached without passing through either of the two preceding stages

STAGE 1 This is the stage of the relatively uncomplicated atheroma. The lesion appears grossly as a grayish white, or more often yellowish, somewhat elevated plaque Its consistency and appearance is somewhat that of the yolk of a slightly more than medium-boiled egg The arterial lumen is at first not narrowed by the plaque, and the heart muscle is both anatomically and functionally perfectly normal

Atheromatous plaques are found in otherwise healthy adult hearts; they may form in any of the coronary arteries (more often in the proximal portions), and they may remain stationary or spread along the borders or begin to bulge into the lumen. The deeper parts of the plaque may degenerate into a soft, mushy, lipid-containing mass, with eventual calcification Sometimes the plaque becomes fibrotic in the absence of much lipoid material The media underlying the plaque usually thins out. Occasionally, the plaque encircles the artery.

Thickening of the arterial wall is not necessarily followed by narrowing of the lumen Aschoff[2] called attention to the dilatation usually seen in the arteries of the aged. Atherosclerosis, according to Duguid,[22] commonly results in widening of the vessels (Fig 25*A*). The arteries are elastic tubes which dilate with each pulsation and then contract, not by muscular action but by elastic recoil When the media adjacent to an atheroma becomes thin, its elasticity is impaired, recoil

A



B



FIG 25 Frozen sections of the same region of the left descending coronary artery from 2 individuals, same magnification (A) A 67 year old man without history of cardiac disease (B) A 31 year old man who died suddenly without any known previous heart attack, but who was said to have complained of indigestion in his last 3 weeks (From Duguid and Robertson [22])

is reduced, and the lumen grows wider This theory would account for the enormous atherosclerosis that is sometimes found at autopsy, with little muscular impairment as revealed by histologic examination, in individuals who during life had no symptoms of coronary insufficiency.

STAGE 2 The plaque may enlarge sufficiently to narrow the lumen by bulging into it (Fig. 25*B*) or by encircling the vessel, in which case it may become *eccentric so that a somewhat* crescentic plaque may partially occlude the artery. In any event, the atheroma must attain considerable size before it interferes with blood flow. Pathologists are often surprised to find extensive damage of vessel walls without concomitant cardiac symptoms or structural changes in the heart muscle The coronary flow may be entirely adequate to the needs of the resting heart, but inadequate to meet an increased demand for blood This is the point at which the first symptoms of angina pectoris become manifest

STAGE 3 With narrowing of the coro*nary arteries, myocardial nourishment is im*paired This must lead to gradual death of tissue, or slow infarction. At any rate, normal muscular tissue is slowly replaced by fibrous tissue, usually in patchy fashion

and confined to the area of the heart supplied by the narrowed arteries. This stage is sometimes referred to as myofibrosis cordis. If the sclerosis is widespread, the fibrosis may be diffuse.

It is a reasonable assumption that each bout of angina pectoris, which in effect is an episode of coronary insufficiency, slightly damages the myocardium, so that fibrosis may result in the long run. In many instances, however, fibrosis may take place without any cardiac pain Decompensation may be the earliest presenting complaint of coronary heart disease

For many years, this stage was known as chronic myocarditis. The identification of this condition as coronary disease, rather than inflammatory disease as implied by its name, represented a great forward step in diagnosis Throughout the stage of slow infarction, a collateral circulation is becoming established, so that the heart suffers less damage than might be expected from the extent of the atheromatous changes in the blood vessels One, two, or even three main arteries may be almost or even completely occluded without the occurrence of acute infarction and even without clinical complaints.

STAGE 4 The stage of acute infarction, which most cases of coronary sclerosis never reach, is usually preceded by Stages 2 and/or 3, and often both concurrently Stage 1 is never skipped, and rarely are both Stages 2 and 3 passed over I have seen no authentic example of direct transition from the first to the fourth stage except when some catastrophe, such as shock, supervened and then only rarely The coronary arteries of patients who suffer an acute infarction after severe hypotension but without coronary occlusion will almost invariably be well into Stage 3

Complete occlusion of the main coronary arteries is not necessarily followed by acute infarction On the other hand, the reverse process—acute infarction in the presence of still open, though narrowed blood vessels—may occur As the vascular lumen narrows, coronary flow may become sharply reduced and yet be sufficient for limited demands Collateral vessels may aid by bringing blood from other parts of the heart, so that just enough blood arrives to provide a very meager subsistence to that area of the heart But when that area suddenly needs more blood, or the blood no longer brings sufficient nourishment, or a critical trickle of blood carried by a small collateral vessel fails to arrive because it is blocked off or there is not enough pressure to push it along, infarction is inevitable despite the patency of the main arteries. The situation is much like that of a man accustomed to good living who is suddenly forced to get along at subsistence level To others, he may seem the same man as before: his outward appearance and behavior, like that of the sclerotic heart, may be unchanged But deprived of the very few pennies he needs for bare survival, he will suddenly and unexpectedly collapse So the damaged heart, which functions when all conditions remain constant, will break down after a seemingly slight change

Infarction in the presence of at least partly patent blood vessels almost invariably denotes severe sclerosis of several arteries. In my experience, infarction does not occur when only a single artery is sclerotic, as it may after complete occlusion of an artery. Even a modicum of blood arriving from somewhere else will keep the integrity of the muscle intact.

COMPLETE ARTERIAL OCCLUSION

CORONARY THROMBOSIS The cause of all infarctions was for a long time considered to be a clot within the artery, and the condition now properly termed myocardial infarction was called coronary thrombosis Today, of course, we know that thrombosis is not the only cause of coronary occlusion, and that infarction and coronary occlusion do not necessarily accompany each other. Nevertheless, thrombosis remains the most frequent cause of sudden, complete blocking of a coronary vessel A thrombus need not occlude an artery suddenly, it may be mural at first and only later occlude completely. Histologically, the older thrombus may be seen next to the vessel wall, with the newer clot adjacent to it[31]

Thrombosis may occur without being followed by infarction Collateral circulation may be adequate to sustain the life of the muscle, or the patient may die too quickly

for infarction to become evident.[87] The thrombus may retract quickly, especially if the vessel wall around it relaxes Figure 25*B* shows this mechanism, the lumen contains an old organized clot which, judging by its shape, originally filled the lumen but then contracted enough to allow blood to pass It has been suggested that the nitrites may be useful in coronary thrombosis by relieving spasm and thus promoting this sort of ameliorative process[20, 21]

The exact frequency of thrombosis is hard to determine An old thrombus, transformed by absorption, organization, canalization, etc, may not be identifiable at autopsy and be passed over as part of the vessel wall The thrombus has even been suggested as the primary lesion[20, 21] Thrombosis of a small but vital collateral channel may result in muscle necrosis, but the cause may not be recognized at autopsy Still another difficulty is that clots formed before and after death are hard to distinguish from each other It was long thought, even by Osler for a time, that clots were formed after or immediately before death and did not contribute to the final cardiac episode

On the basis of autopsy studies, thrombosis is the responsible factor in about half of the reported cases of infarction. In one series of 80 cases, all soldiers under the age of 35, recent clot was found in 29[27] In another series, also of young patients, less than one third of the cases had thrombosis[54] Thrombosis was found in 45 per cent of patients dying of coronary disease, more often in those with hypertension,[14] another report gives the figure of 61 6 per cent of the cases.[81] Among 126 fatal cases of acute myocardial infarction, thrombosis was present in 54 4 per cent,[59] of 45 instances of coronary "occlusion," 32 had thrombosis[71]

Several theories attempt to explain why thrombi form and why they are found exclusively at the site of atheromatous plaques

1. Stasis and eddying of the blood at the site where the intima is raised by a plaque[30] This factor is probably of some importance in cases in which the endothelium is intact and the intimal lesion has not undergone recent change. Reduced blood flow in acute hypotension and heart failure, or increased viscosity of the blood, may be contributing causes.

2. Acute inflammatory changes in the intimal lesion.[11, 59]

3. Breaks in the plaque surface. Rupture of an "atheromatous abscess," especially in the aged, is thought to be a frequent event,[11] in 32 instances of thrombi, all were located on "atheromatous ulcers"[71]

4. Presence of fibrinoid material. This material may be found in a plaque with an overlying clot. Its relation to thrombus formation is so far purely conjectural.

5. Hemorrhage into an atheroma Such a hemorrhage is frequently found beneath a thrombus, and presumably bears some causative relation to it

COMPLETE OCCLUSION BY ATHEROMA

A coronary artery may be completely blocked by atheroma both in chronic and in acute infarction In recent infarction it is almost invariably associated with more or less severe sclerosis of other coronary arteries Multiple atheromatous occlusions of the same vessel are often encountered.

INTRAMURAL HEMORRHAGE

The intima normally contains no blood vessels, but the intima of a diseased artery has capillaries, most of them near the intima and some immediately beneath the endothelium The more fibrous an intimal lesion is, the greater the vascularization; large atheromatous plaques with wide cholesterol clefts have the fewest vessels.[50] Rupture of the intimal capillaries may be caused by one or more of the following[61] *(1)* increased pressure within the capillary lumen, *(2)* increased fragility of the capillary wall, as in vitamin C deficiency; *(3)* diminished support from the surrounding atheromatous tissue

The most common etiologic factor in increased intracapillary pressure is permanent or temporary hypertension Unlike other capillaries, the intimal capillaries do not lie at the end of a long series of arteries or arterioles which absorb much of the pressure; they communicate directly with an artery in which the blood pressure is relatively high, approximating that of the ascending aorta Intimal hemorrhage occurs five times as often in patients with hypertension as in those with normal blood pressure, according to Patterson, he suggests that transient hypertension may be responsible for hemorrhage,

especially in cases of sudden strain or injury.

Inadequate support of the capillaries by the surrounding degenerated, atheromatous, softened tissue allows the intracapillary pressure to dilate its walls to the point of rupture, in such cases, calcification of the abscess is a protective mechanism On the other hand, it is also believed that the intimal vessels are adequately supported by collagen bands[56] Another possible mechanism, proposed by Roberts,[63] is: "Angulation of a semirigid coronary artery by the beating of the heart would in time cause excessive bending, stretching and then rupture of these subintimal vessels"





FIG 26 Occlusion of coronary artery by intramural hemorrhage (Left) Section through descending branch of the left coronary artery, a, massive hemorrhage into vessel wall, b, intact endothelial lining c, patent lumen (Right) Section 3 mm distal to left figure, a, intramural hemorrhage, b, intact endothelial lining and absence of thrombus, c, lumen occluded by hemorrhage (From Wartman[86])

A vicious cycle of hemorrhage→healing →new vessels in granulation tissue→hemorrhage may thus be created[56] Younger capillaries, such as are found in fresh granulation tissue, are more fragile and therefore are more likely to rupture than older ones[11] The hemorrhage may be so large that complete occlusion may result even without a break in the endothelial lining of a formed thrombus In a series of 41 completely blocked coronary arteries, 6, or 14 6 per cent, were the result of intramural hematoma alone[56] (Fig 26). The importance of serial sections is stressed, for otherwise an old lesion, consisting only of a residuum of hemosiderin in a plaque, may be mistaken for a canalized thrombus. In all 6 of Wartman's cases, the coronary arteries showed advanced atheromatous lesions, and the hemorrhage was usually into an atheromatous plaque Bleeding never extended into the media, but multiple small hemorrhages were scattered throughout the intima in most of the cases, especially beneath the endothelium. Focal accumulations of red cells surrounding the capillaries vascularized the intima in the region of the hematoma. The cells were frequently intact, indicating fresh hemorrhage, in some cases there was lysis and beginning organization and pigmentation. No clinical signs distinguished these cases from those of ordinary coronary thrombosis, some patients died suddenly, others more gradually Still another mechanism may cause occlusion without thrombosis irritation and spasm of the media from a small and otherwise innocuous hemorrhage.[61]

Several reports have described a break in the endothelial lining of a coronary artery just beneath a thrombus.[5, 13, 39, 42] Such breaks in the intima may be related to thrombus formation[5, 39] Rupture of an atheromatous "abscess" plays a role in the pathogenesis.[42] In a study of the pathology of coronary thromobosis, a fresh break was commonly found in the fibrous lining of a lipoid plaque, with blood elements penetrating into the atheroma, in some cases, there was thrombus formation on an atheromatous

plaque in which thinning out and separation of the fibers in the plaque's lining also permitted infiltration of blood elements.[13] In a series of 41 occluded arteries, 14 showed a combination of intramural hemorrhage and thrombosis[56] Patterson,[61] who firmly believed that intramural hemorrhage and overlying thrombosis were related, suggested that an intimal hemorrhage may produce occlusion: (*1*) by initiating a coronary thrombus, which is the case in most instances; (*2*) by a large occluding hemorrhage without thrombosis, found in 13 per cent of cases, and (*3*) by causing coronary spasm Intramural hemorrhage need not result in complete occlusion of the coronary vessel. In about a third of such cases, there is only increase in the size of the plaque, first from the added blood and then by the products of repair

The appearance of the lesion may not reveal whether intimal hemorrhage has occurred, with subsequent rupture into the lumen and thrombus formation, or whether the intima ruptured first, with extravasation of blood from the lumen into the intima Wartman[56] believed the former to be the more likely

If it be assumed that the thrombus formed first, then it is difficult to explain the formation of a hematoma in the wall of a vessel, because, if the occlusion were complete, no blood could reach the affected portion, or, if the occlusion were only partial, it would seem logical to assume that the mural thrombosis would protect the intima and tend to prevent the development of a hematoma Again in some of the cases which have been studied, the hemorrhage within the vessel wall is of greater age than the thrombus as indicated by the finding of hematogenous pigment within phagocytes and of beginning organization, whereas the thrombus shows none of these features

Intramural hemorrhage may possibly be of inflammatory rather than degenerative origin. Acute inflammatory reactions in the intima have been found in 2 cases of fresh coronary occlusion.[11] Of 11 cases of coronary occlusion associated with intimal hemorrhage, syphilitic changes were the cause of the hemorrhage in 1 case.[56] The patient was a 34 year old woman who died suddenly, her right coronary artery, the one usually involved in syphilis, was completely occluded by the hemorrhage.

There seems little doubt that such hemorrhages are found in a fairly large number of coronary occlusions Thus, in one series there were 12 per cent,[94] in another, hemorrhages within atheromatous fibrous plaques were found in almost all patients who died suddenly of coronary disease and were below the age of 60.[23] These hemorrhages were usually multiple and varied in age from fresh bleeding to areas of iron-containing pigmentation. The thrombi occurred more often with old than with fresh hemorrhages Intramural bleeding with overhanging thrombus was found in 16 7 per cent of 126 cases of recent infarction[59] Indeed, this lesion has even been called "the commonest mechanism of complete occlusion of the lumen of a coronary vessel.[44] Intimal hemorrhages of varying degrees were found in 54 of 135 cases of coronary disease.[25]

CORONARY COLLATERAL CIRCULATION

The normal circulatory path of the blood in the heart is aorta→coronary artery→capillary→coronary vein→right side of heart. About 60 per cent of the blood in the intracardiac circulation follows this path through the coronary sinus (Fig 27) About 40 per cent flows along other pathways, sidetracking the capillaries, the coronary veins, the coronary sinus, or all of these. In the simplest variation, some blood is brought straight back to the heart chambers, especially on the right side, through the coronary veins which empty directly into the cavities instead of via the coronary sinus Venous blood may return via small venules and capillaries which may form a direct connection between the small veins and the auricles and ventricles, providing a quick way for getting blood back to the heart without its getting into the larger veins. This system, properly known as the thebesian system, is distal to the capillary bed, in contrast to the vessels of Vieussens, which go from the arterioles into the heart chambers without involving the capillary circulation Some feel that it is difficult to distinguish the arterioluminal vessels of Vieussens from the venoluminal vessels of Thebesius[70] Comparatively little is known about the vessels of this large intramyocardial network—whether they are always capillary, arteriolar, or venular in size, whether they

communicate with each other, and how they communicate with the intramural system of arteries and veins. The thebesian vessels are found principally in the right side of the heart. They are also fairly numerous in the left ventricular wall, but are rare in the left auricle. This agrees with Thebesius' concept that the function of the system is the rapid drainage of venous blood from the myocardium. On the right side of the heart, a thin and highly trabeculated wall with relatively few veins provides the short route necessary of the spongy spaces in the embryonic myocardium, are larger and more irregular than capillaries, and their walls consist of single layers of endothelium The arterioles break up and enter the sinusoids; the latter anastomose freely with other sinusoids and capillaries, and enter directly into the cardiac chambers, usually deep within the intratrabecular spaces Direct shunting from the arteriole to the venous side of the circulation by way of arteriolar-venous vessels is possible, but is rare and probably unimportant [89]

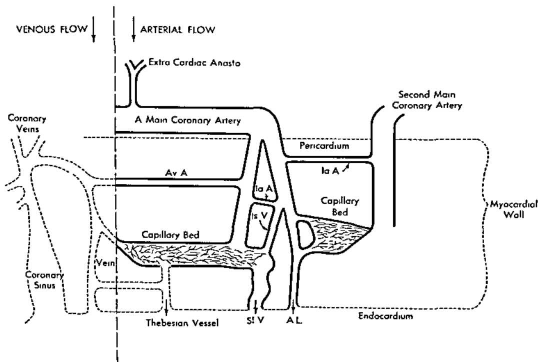


FIG 27. Collateral circulation of the heart A L, arterio-luminal vessels, Av A, arteriovenous anastomoses, Ia A, interarterial anastomoses, Is V, arterio-sinusoidal vessels Sl V sinusoidal luminal vessels

for the return of blood to the heart cavities, on the left side, there is a thick ventricular wall, with its definite and efficient system for the relatively long route back to the right side

One method of bypassing the coronary sinus avoids the capillary and venous systems entirely, the blood being carried back to the heart chamber via the small (arteriolumınal) vessels just mentioned, which connect the arterial branches with the heart cavities The arteriosinusoidal vessels, described by Wearn and associates,[90] are another means of shunting the venous blood These myocardial sinusoids, probably relics

These vessels may be of fairly large caliber, glass microspheres as large as 75μ in diameter, and therefore too large to pass through the capillary circulation, return through the coronary sinus when injected into a coronary artery. Although not conclusive, this experiment seems to demonstrate some sort of arteriolar-venous shunt

ARTERIOARTERIAL SHUNTING

It has long been conceded that the muscular area supplied by an occluded artery may be nourished by collateral vessels derived from other coronary arteries While such collateral arterioarterial channels may exist

in the normal heart, it is unlikely that they function except under special conditions.

An arterial anastomotic circulation normally connects capillaries and other very fine branches,[31] and some believe that with advancing age anastomosis occurs between large precapillary vessels.[31, 80] Whether larger interarterial communications are active during life is not known, but there is little doubt that they are potentially active or can quickly develop This is amply demonstrated by the fact that watery solutions injected into one coronary artery are always found in the others Since particles of lead agar suspension of 40μ diameter did not pass through, it was inferred that collaterals of this caliber or larger are not normally present in the human heart But an experiment using a lighter opaque material containing red blood cells seemed to show that the collateral channels are large enough to accommodate red blood cells easily, the presence of collaterals between one large artery and another seemed likely, although they might be smaller than 40μ diameter.[9, 64, 74] The existence of interarterial communications may therefore be safely assumed, although effective flow through these channels is probably absent until the pressure in a coronary branch is sufficiently reduced through narrowing of the artery [91]

In summary, then, the normal heart has a few collateral vessels, mostly of capillary size, others, somewhat larger, do not function ordinarily but may be useful in time of trouble.

In effect, the coronary arteries are end arteries during health In young persons, sudden occlusion of a major vessel can be and often is abruptly fatal. The lesion in such patients is frequently confined to a single vessel, or sometimes to a small part of a single vessel, and the heart has not yet braced itself for a major occlusion by developing a collateral circulation

Fortunately, since atheromatosis is a slow process, there is usually time for a collateral circulation to develop, so that incomplete or complete occlusion of a major vessel need not be an unmitigated disaster Sclerosis and development of anastomoses is a simultaneous process, and there is little evidence of trouble until the degree or speed of the occlusion outstrips the compensatory ability of the new circulation

Recent studies[79] indicate that the collateral circulation is of greater importance in curtailing the extension of the infarct than in preventing tissue necrosis itself if a major vessel is occluded. In contrast to earlier findings of other investigators,[9] it was found that a major coronary occlusion is almost invariably followed by infarction, but that the size of the affected area is controlled by the effectiveness of a collateral circulation

DEVELOPMENT OF COLLATERAL CIRCULATION

An adequate collateral circulation is brought into existence either by the opening of pre-existing but nonfunctioning channels or by the formation of new vessels Several factors favor the development of a collateral circulation

1 Almost certainly, pressure gradient changes in coronary arteries are mainly responsible for opening dormant shunting channels or establishing new ones Previously empty interarterial vessels fill with a stream of blood flowing toward the occluded artery, especially its peripheral end Changes in intramural and intraventricular pressure relationships may also account for a reversal of blood flow, if any, from the heart chambers to the coronary arteries

2. Release of histamine or some other metabolic product, such as a nucleic acid derivative, in or at the borders of an ischemic area of myocardium, may possibly stimulate the dilatation or establishment of neighboring collateral vessels This hypothesis is as yet almost purely speculative The development of new vessels as the result of biotactic reactions may have some such explanation [13]

3 Relative cardiac anoxia, whatever means produce it, stimulates formation of anastomoses Anemia, cor pulmonale, pulmonary emphysema, cyanotic congenital heart disease, all induce the development of new channels Anoxia is the most powerful coronary dilator known and causes an increase in collaterals, whether "by increased cardiac work, coronary artery insufficiency or decrease in the amount of circulating oxygenized hemoglobin."[95] Increasing anastomoses have been noted in the following conditions, in the ab-

sence of coronary disease, rheumatic valvular disease, congenital cardiac malformations, hypertension, bronchial asthma, obesity, and anemia; it is assumed that the anastomoses were the result of a response to increased myocardial demand.[51]

4. Other factors may be neural (reflex) mechanisms, increase in venous pressure, as by ligation of the coronary sinus, and new channels through adhesions, etc.

The possible routes for a compensatory collateral circulation are (*1*) interarterial communications, (*2*) extracardiac anastomoses, and (*3*) reversal of blood flow.

INTERARTERIAL COMMUNICATIONS This may occur in occlusion of the left anterior descending artery. The blood leaving the aorta then enters the right artery or the left circumflex branch, and some of this blood passes via channels which connect arterioles to the ischemic area formerly supplied by the occluded artery. It has been estimated that from 25 4 cc. to as much as 105 cc of blood per minute may flow through the peripheral end of an occluded artery The average amount of blood diverted to ischemic areas is about 4 to 4 5 per cent of the total flow through a main artery. Furthermore, if the descending or circumflex arteries are occluded, 64 per cent of their collateral flow will originate from other coronary arteries. About 87 per cent of the collateral flow to an occluded right coronary artery will originate from the left coronary, which means that a substantial portion of the compensatory flow must be derived from other sources It is probable that the number and usefulness of these intercoronary anastomoses vary considerably.[50]

Three pathologic types of interarterial anastomoses have been distinguished.[72] (*1*) connections between two branches of a coronary artery or those bridging a gap between two parts of the same vessel, (*2*) complete dependence of the vessels distal to an occlusion on another coronary artery for their blood supply, (*3*) "convergent anastomoses," in which one or more arterial branches receive blood from both coronary arteries

Interarterial communications between main coronary arteries are found in greater number. (*1*) in the anterior portion of the right ventricle, to the right of and parallel to the anterior interventricular groove, (*2*) in the region of the posterior interventricular groove, and (*3*) in the interventricular septum.

EXTRACARDIAC ANASTOMOSES First described by von Haller,[12] these branches were largely overlooked until Wearn and associates[90] once more brought them to attention Anastomoses were found between extracardiac organs and the coronary arteries through their pericardial fat branches, which leave the heart around the aortic orifices, pulmonary arteries and veins, venae cavae, and in the interventricular pericardial reflections These branches anastomose extensively with the pericardiophrenic branches of the internal mammary arteries and the anterior mediastinal, pericardial, bronchial, superior and inferior phrenic, intercostal, and esophageal branches of the aorta The channels, though of small caliber, are numerous, and collectively may form a fairly large anastomotic channel The normal direction of blood flow in these vessels is not known so far, nor is it certain whether they constitute a useful compensatory pathway. Anastomotic channels are sometimes found in the pericardial adhesions which form after myocardial infarction, but they are by no means constant and there is no evidence as yet that such channels help to sustain myocardial viability Animals have lived after ligation of a coronary artery and vein, but promptly succumbed to cardiac failure when the extracardiac anastomoses were severed[69, 70] The possibility of routing blood back to the heart through such extracardiac anastomoses is the basis of one type of operation proposed for the treatment of coronary heart disease.

REVERSAL OF BLOOD FLOW This is the last possible means of compensatory nourishment of an ischemic area, and permits the heart wall to be nourished directly from the cardiac cavities. Under such circumstances, the blood would flow through the thebesian, arteriololuminal, or sinusoidoluminal vessels toward the heart wall. Particulate matter injected into the ventricular cavities was found in the capillaries of the ventricular walls even when there was no possibility of its getting there through the coronary arteries[37]

Some believe that reversed blood flow through thebesian vessels is extremely unlikely.[69, 70] When the coronary ostia are occluded, the pressure gradients may permit flow from the ventricle into the luminal vessels and sinusoids.[91] Pressure differences between the right and left ventricles determine the direction of flow in the luminal vessels on the right side of the heart When the pressure in the left ventricle is greater than in the right, there is no significant flow toward the heart wall; however, when the right ventricular pressure *is greater than the left, the blood flows into* the luminal vessels and toward the coronary arteries.

Robertson[70] at one time felt that such a reversal was most unlikely and theoretically groundless The most favorable time for such a flow would be in auricular systole, when the intraventricular pressure is rising but the coronary inflow is falling off This is just the time when the pressure within the heart wall is rising and venous blood is about to be ejected. If the contraction of the wall in an ischemic area is weak, conditions for reversal of flow should be somewhat better. Robertson found that a thebesian reverse flow, if it occurred at all, was not sufficient to maintain life in an animal with a ligated coronary artery and with severed extracardiac communications This was true even when the coronary sinus was ligated to increase the venous pressure and dilate the thebesian veins.

There is therefore ample evidence to indicate that, at least theoretically, it is possible for the heart wall to receive some of its blood supply from the ventricular cavities.[90] No evidence, however, exists that such a flow does or can take place on the left side of the heart, where infarctions are most common. Even could venous blood somehow be brought back to the heart, it is highly improbable that such blood, with its low oxygen and high carbon dioxide contents, would be of any use in nourishing poorly vitalized tissues. Flow of blood from the right auricle to the coronary sinus toward the heart wall is anatomically possible, but there is no evidence that it occurs.

SPEED OF DEVELOPMENT OF COLLATERAL CIRCULATION

In other carefully studied regions of the [illegible] collateral circulation is set up with remarkable speed. Occlusion of the femoral or carotid arteries results in an almost immediate increase of peripheral arterial pressure and retrograde flow. High values are soon observed, and a pulse appears within a few hours or days [30] In the coronary arteries, the process is a more leisurely one. When a coronary artery is suddenly occluded, the ischemic area ceases to contract in about 1 minute, this would not occur were an effective collateral vessel ready to take over at once.[83] The retrograde coronary blood flow *after abrupt occlusion is approximately only 0 5 to 5 8 cc. per minute,*[21] *and many days* elapse before the value of 30 to 40 cc is reached [30]

The collateral circulation is ineffective early in acute coronary occlusion,[91] 2 to 3 weeks are probably required for a functionally significant collateral circulation to develop [8] Experiments on the domestic pig, which, unlike the dog, does not have relatively large interarterial connections, emphasize the slow development of collaterals after acute occlusion Nevertheless, there is probably some early effective collateral circulation, since infarcted areas are generally smaller than the mass of muscle supplied by the occluded vessel [9]

The clinical importance of this is obvious If the oxygen demands of the myocardium can be reduced by decreasing the work of the heart (*i.e*, clinical rest) until the collateral circulation is well developed, infarction may be prevented, provided the ischemic area is relatively small *But* when the metabolic demands of the heart are increased by exercise, valvular disease, or hormonal stimulation during the time when the compensatory flow is still small, death of heart tissue is much more apt to occur.

MYOCARDIAL LESION

When the heart stops shortly after complete occlusion of a coronary artery, there may be no pathologic changes in the myocardium In most cases, however, myocardial infarction will occur, provided the involved artery is large enough and the occlusion is sudden. Obviously, the exact sequence of events, especially the time sequence, cannot be observed in man *in vivo* While some analogies may be drawn from the experimental ligation of coro-

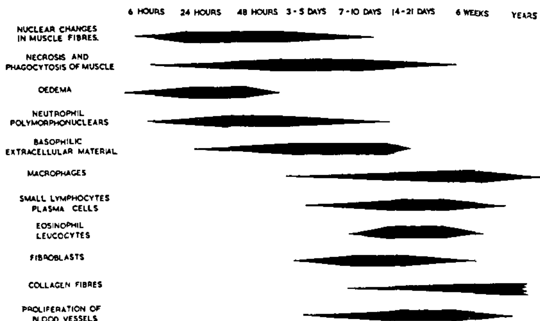


FIG 28 Character of cellular exudate at various stages after cardiac infarction (From Lodge Patch[46])

nary arteries in animals, they must not be pushed too far. In man, occlusions generally occur in a vascular tree which is the site of atheromatosis, often of the most advanced degree. Conditions in experimental animals, with one ligated artery and the rest apt to remain normal, are not comparable. Furthermore, the canine heart has freer arterial anastomoses than does the heart of man,[16] it is therefore scarcely surprising that infarcts seem to heal more rapidly in the dog than in man. Compared with the long, detailed investigation of coronary artery lesions, myocardial changes have had little study In many cases, the exact time of onset of the infarction is difficult to establish, until the careful studies of Willius,[92] of Mallory and co-workers,[47] and of Lodge-Patch,[46] little was known of the sequence of pathologic changes in the myocardium (Tables 7-8, Fig 28). The description that follows is largely based on these studies

During the first 3 days, gross detection of an area of infarction may be difficult The first noticeable change is that the muscle is paler and dryer than normal, with occasional

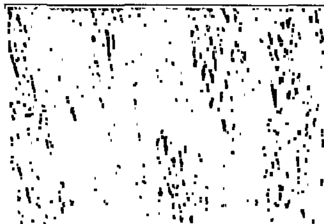


FIG 29 Myocardial scars resulting from coronary sclerosis (From Bell[4])

TABLE 7. HISTOLOGIC FEATURES OF MYOCARDIAL INFARCTS IN MAN IN RELATION TO TIME

	Hours			*Days*										
	9	*12*	*40*	*2*	*3*	*4*	*5*	*7*	*9*	*10*	*13*	*15*	*34*	*35*
		+	+											
Congestion and interstitial edema	+	+	+	+	+	+								
	+	+	+	+	+	+	+							
	+	+	+	+	+	+	+	+	0	0	0	0	0	0
			+	+	+	+	+							
Necrotic muscle			+	+	+	+	+	+						
			+	+	+	+	+	+	+	+	+			
	0	+	+	+	+	+	+	+	+	+	+	+	0	0
			+	+	+	+	+							
Nuclear degeneration			+	+	+	+	+							
	+	+	+	+	+	+	+	+	+	+	+			
	+	+	+	+	+	+	+	+	+	+	+	+	0	0
				+	+									
Polymorphonuclear leukocytic infiltration			+	+	+	+								
			+	+	+	+	+							
	+	+	+	+	+	+	+	+	+	+	+	+	0	0
											+	+		
Plasma cells and lymphocytes								+	+	+	+	+	+	+
	0	0	0	0	0	0	+	+	+	+	+	+	+	+
											+	+	+	+
Pigmented macrophages							+	+	+	+	+	+	+	+
	0	0	0	0	+	+	+	+	+	+	+	+	+	+
											+	+	+	+
Fibroblasts and scar tissue								+	+	+	+	+	+	+
								+	+	+	+	+	+	+
	0	0	0	0	0	+	+	+	+	+	+	+	+	+
													+	+
Collagen													+	+
													+	+
	0	0	0	0	0	0	0	0	0	0	+	+	+	+

From Cook [16]

hemorrhagic areas. On the fourth day, a fine yellow border, the result of leukocytic infiltration, can be distinguished; this area becomes broader and may turn somewhat greenish by the sixth to the eighth day. A reddish purple zone around the infarct appears after 8 to 10 days, the result of many newly formed capillaries. As muscle fibers die off, the myocardium becomes thinner, and a definite depression can be seen in cross section. With time, the central area of dead tissue decreases, and only small islands, completely surrounded by granulation tissue, are found after 3 to 4 weeks As the granulation tissue grows older, it becomes paler and more gelatinous, due to an increase in collagen content and the compression of capillaries At 2 to 3 months, *the infarct is shrunken, white, and* fibrous; thereafter little change is found (Fig 29). The pericarditis, which in the early stages

TABLE 8. RELATION OF AGE OF INFARCT TO HISTOLOGIC FEATURES

Age of infarct	Necrosis	Polymorphonuclear leukocyte infiltration	Blood vessels, connective tissue	Removal of fibers	Pigmented macrophages	Eosinophils	Plasma cells, lymphocytes	Collagen
1 day	++	+	0	0	0	0	0	0
2 days	++++	++	0	0	0	0	0	0
3 days	++++	+++	0	0	0	0	0	0
4 days	++++	++++	0	0	0	0	0	0
5 days	++++	++++	+	+	0	0	0	0
6 days	++++	+++	++	+	+	+	+	0
7 days	+++	++	++	+	+	+++	+	0
2 weeks	++	+	+++	+++	+++	++++	+++	+
3 weeks	+	+	+++	+++	++++	+	++++	++
4 weeks	+	0	++++	++	++++	0	++++	++
2 months	+	0	++++	+	+++	0	+++	+++
3 months	+	0	++++	+	+++	0	+++	++++
4 months	0 to +	0	++++	?	++	0	++	++++
5 months	0 to +	0	++++	?	+	0	+	++++
6 months–1 year	0	0	++++	?	+	0	+	++++
1 year and over	0	0	++++	?	+	0	0	++++

From Mallory *et al*[47]

was manifest as a thin, easily detached layer of fibrin, has by this time turned into a white area of fibrosis

The microscopic features are necrosis, hemorrhage, leukocytic infiltration, connective tissue formation, and removal of dead tissue Presumably, necrosis of the muscle fibers, and to a smaller degree of the blood vessels and supporting structure, starts at once, but the first anatomic changes are observed after 5 or 6 hours. The muscle fibers then appear more hyaline and stain deeply; *they may be swollen and contain variously* sized eosinophilic granules or large, irregular cross bands The striations do not disappear entirely, dead tissue is gradually removed, but some fibers may persist for months The necrosis is fairly uniform throughout the area of infarction, although there may be a layer of surviving tissue 0 3 to 0 5 mm thick along that portion of the endocardium accompanying the thebesian vessels into the myocardium

HEMORRHAGE Only rarely are myocardial infarcts purely anemic or purely hemorrhagic. Focal hemorrhagic areas are found frequently, diffuse hemorrhage is rare, as is extravasation around the muscle fibers. The erythrocytes are found in distended venules and capillaries, eventually, the cells break up and the hemosiderin is removed by macrophages

POLYMORPHONUCLEAR LEUKOCYTE INFILTRATION Leukocytes appear on the first day at the border of the infarct At first they are present only in the interstitial tissue and around the blood vessels, later, they spread in various directions, including, to a limited degree, the necrotic muscle fibers They do not penetrate deeply, so that the central area of larger infarcts is not infiltrated The polymorphonuclear leukocytes increase in number for about 4 days, some show degeneration, blurring of outline, and nuclear fragmentation as early as 48 hours, by the fourteenth day, however, all have disappeared Exactly what role these cells play in infarction is not known They have no function which can be recognized histologically, they do not phagocytize dead tissue, but they may produce an enzyme of importance in the healing process Eosinophils in varying number

may be found in the infarct from the fourth to the eighteenth day.

NEW BLOOD VESSELS AND CONNECTIVE TISSUE Small, newly formed blood vessels grow in from the periphery toward the center after the fourth day. In some infarcts, however, the central area remains poorly vascularized. Basophilic fibroblasts, often with mitotic figures, accompany these blood vessels and are present in infarcts 4 to 23 days old Unlike infectious lesions, fibrin is not the stimulus for this ingrowth, for little fibrin is found. Newly formed collagen fibers are present at about 12 days. At 3 weeks, the collagen is prominent at the periphery, and at 2 to 3 months it has reached its maximum This collagen increases the strength of the fibrous scar

REMOVAL OF NECROTIC TISSUE Simultaneously with the ingrowth of blood vessels and connective tissue, mononuclear cells, probably histiocytes, begin to remove necrotic tissue at the periphery. These cells penetrate the fibers and phagocytize them. The fragments may be seen within the cell, but eventually disappear, apparently as a result of complete dissolution. Part of the lipofuscin is removed by these cells, but numerous pigmented macrophages may be found in the infarct. Some of the macrophages may also have iron-containing pigment from broken-down erythrocytes These cells may be present for months, but are not usually found in infarcts which are more than a year old. Foci of lymphocytes and plasma cells appear at about the same time as the macrophages, but are never as numerous

LIPID The presence of fat depends largely on the suddenness of the occlusion. When the infarcted muscle is the site of prolonged ischemia due to gradual reduction in the blood supply, fatty degeneration occurs The amount of fat decreases with increasing age of the infarct.

CALCIFICATION Old infarcted areas may contain deposits of calcium, sometimes massive[7] True bone formation has been reported in a few cases.[16]

PERICARDITIS If pericarditis occurs at all, fibrin can be found after 24 hours. Organization of the fibrin begins after the eighth day and is complete by about 4 weeks

MURAL THROMBI Organization of mural thrombi begins on about the ninth day and is complete on the sixteenth day. Fresh thrombi, presumably due to cardiac dilatation, are sometimes found in old infarcts

Cook's[18] findings, in a study of 20 patients and 13 dogs, were much the same as the foregoing description (*see* Table 7). The healing process in both was generally very similar. No Karsner foreign-body giant cells were found in the human lesions Hemorrhage was more prominent in the experimental lesions, and they tended to heal much more rapidly Blood vessel and connective tissue proliferation appeared on the fourth day in the human lesions, fibrosis and contraction were found after the third week.

The findings of Mallory and associates have on the whole been confirmed by Lodge-Patch He, too, reports that during the first week, the histologic picture reveals the age of an infarct with an accuracy in a range of 4 hours, in the later stages, the age of the lesion cannot be estimated quite so accurately.

LOCALIZATION OF INFARCT

RELATION TO CARDIAC MUSCLE BUNDLES Anatomists have long recognized that the ventricle is made up of several separate muscles, but not until the careful investigations by Robb and Robb[65-67] did clinicians and pathologists recognize the importance of this fact. The following description is based on their reports and those of Miale and Bledsoe[51] and of Wartman and Souders[88] Two factors which make study of the muscle bundles difficult are: (*1*) the heart muscles lack fascia and there is some interlacing, and (*2*) occasional variations in the normal pattern

The muscular bands of the heart, consisting of two superficial and two deep muscles, are remarkably constant, and with only occasional variations are found in all hearts Mall named those that originate from the left (aortic, bulbar) side of the heart the superficial (SBS) and deep (DBS) bulbospiral muscles, those from the right

or venous side, the superficial (SSS) and deep (DSS) sinospiral muscles A fifth muscle, the scroll muscle, may be added to these.

The superficial muscles originate near the mitral and tricuspid orifices and spread downward, forming a superficial layer about 1 mm thick over both ventricles, except at occasional points near the base of the heart where the DSS can be seen through fenestrations At the apex, the fibers form a vortex and penetrate to the interior of the ventricles, there they lie under the endocardium, spiraling upward and surrounding both ventricular cavities, to attach directly or indirectly to the tendons around the auriculoventricular orifices

The auricles, the left ventricular apex, and the interventricular septum are formed entirely by the superficial muscles

Superficial Bulbospiral Muscle The SBS arises from the conus tendon, the pulmonary root, the left trigonum fibrosum, and the anterior, lateral, and posterior curvature of the left atrioventricular ring. The origin of the muscle varies somewhat, but it invariably covers at least the apical two thirds of the left ventricle and one third of the right ventricle It spirals downward to the apex, penetrating it and forming the inferior (posterior) papillary muscle in both the right and left ventricles In its intramural portion, it encircles the apex of the left ventricle once, forming the posterior portion of the lower third of the septum In the right ventricle, it gives many fibers to the anterior papillary musle and a few to the left papillary muscle

The blood supply of this muscle is derived from various sources Several superficial twigs from branches of the left circumflex artery supply the anterior and lateral regions of the first part. The fibers at the conus receive their blood supply from the first branch of the right circumflex artery or from proximal branches of the anterior descending artery In 85 per cent of cases, the posterior superficial and papillary portions are supplied by the right coronary artery, less often, by the left or a combination of both.

An experimental lesion of any part of the muscle produces depression of the R-T segment in lead I and R-T elevation in leads II and III of the electrocardiogram

Superficial Sinospiral Muscle The SSS arises around the tricuspid area and spirals downward, covering most of the basal portion of the right ventricle posteriorly and much of the right ventricle anteriorly Its second part plunges deeply to encircle the left ventricular apex, here contributing the anterior lower third of the septum The third portion of this muscle becomes the anterior papillary muscle. The blood supply of the first part consists of superficial twigs of the right circumflex artery and the right lateral branches of the left anterior descending artery; the second and third portions are supplied by the distal third or less of the left anterior descending artery

Experimental lesions produce elevation of the R-T segment in all three leads, with concomitant T wave negativity

Deep Sinospiral Muscle The DSS originates from the circumference of both atrioventricular rings It encircles both ventricles horizontally and surrounds the basal two-thirds of the left ventricle. Toward the apices there is a deficiency of muscle, the gaps being filled in by the superficial muscles. The descending branches of the right circumflex artery supply the right part of the DSS, the first large left collateral branch of the left anterior descending artery and descending twigs of the left circumflex artery supply the left portion; penetrating branches of the anterior and posterior descending arteries supply the septal portions of the muscle Occlusion of the proximal portion of the left anterior descending, of the beginning of the left circumflex, or of the right circumflex arteries will therefore involve the DSS

Experimental lesions produce an elevation of the R-T segment in lead I and a depression of the R-T segment in lead 3 Involvement of the septum will result in a deep Q wave.

Deep Bulbospiral Muscle The DBS is confined entirely to the left ventricle. The muscle forms a strong circular cuff surrounding the mitral orifice and the aorta The muscle fibers form three interweaving bands Branches of the left coronary artery supply the blood for this muscle

Physiology Each of the ventricular muscle bundles apparently has specific functions The two functions of the superficial muscles are: (*1*) fixation of the apical fulcrum so that the septum and the weak-walled apices do not bulge during systole, (*2*) fixation of the auriculoventricular valve leaflets, thus preventing regurgitation into the auricles during systole Development of a mitral murmur after apical infarction may be explained by the inadequate tension of the damaged muscle on the valves, rather than by dilatation of the fibrous rings at the base of the heart

The DSS, which forms the main mass of the right ventricle, has an expulsive function and is probably responsible for maintenance of the pulmonary circulation The left portion of the muscle, together with the DBS, probably empties the left ventricle Injury of either portion of this

muscle causes a drop in blood pressure.

The DBS helps to expel blood from the left ventricle and is essential in maintaining the aortic pressure toward the end of systole. Experimental injury of both superficial muscles and/or the deep sinospiral muscle is compatible with survival, but the animal dies if the deep bulbospiral muscle is damaged.

Infarction often follows the muscle bundles with little overlap. Occasionally, only part of the muscle circumference is involved; the subendocardium may be involved, while the subepicardium remains uninvolved, or the posterior portion of the deep bulbospiral muscle is damaged but not the anterior. The superficial muscle bundles are more often affected than the deep muscle bundles. The deep sinospiral muscle is the one least affected, and right-sided infarction is therefore uncommon.

No constant relation has been established between the artery occluded and the site of an infarct. In general, however, occlusion of the right coronary artery leads to infarction in the deep muscles, especially the posterior and basal portions, disease of the left anterior descending artery affects both superficial muscles, anterior and apical portions, while involvement of the circumflex artery affects either the deep or superficial bundles.[88] In a series of 72 cases, three types of infarction were distinguished, and their frequency noted: (*1*) full thickness, involving two or more muscles except at the left apex, where only one muscle may be involved (27 cases); (*2*) massive, extending through a large part of wall and always involving at least two muscles (29 cases); (*3*) laminar, usually involving only one muscle (16 cases). Cardiac rupture was found only with full thickness infarcts, often when old and new infarcts were in the same place. No case of rupture was found with old infarction alone. Aneurysm occurred twice as often in full thickness infarcts as in both other types combined.

LOCATION OF CORONARY OCCLUSION

Most coronary occlusions occur in the proximal parts of the main coronary arteries, within the first 4 cm. of the left or right coronary vessels, or the first 2 cm. of the left anterior descending branch or the left circumflex artery. The older the patient, the more likely is multiple involvement in any combination of vessels affected.

The most vulnerable artery by far is the left coronary. The first 2 cm. of the left anterior descending branch constitute in effect the heart's death trap. Some idea of the magnitude of the percentages involved may be gained from a summary of 1,465 occlusions from several sources:[1, 26, 28, 85, 87]

Site	*No. of occlusions*
Left main artery	71
Left anterior descending branch	834
Left circumflex artery	211
Right main artery	379

There is no constant relation between the site of infarction and the artery occluded. Among the determining factors are the narrowing of other vessels, the effectiveness of collateral vessels, and variations in the distribution of arterial blood. Occlusion of a small vessel may, by reducing the total flow to a given area below a critical level, cause "infarction at a distance."

Almost all infarctions affect the left ventricle. "Pure" right-sided infarction is exceedingly rare, accounting for about 2 per cent of all cases, almost invariably, necrosis of the right side is an extension from the left. Whether there is any area of predilection for infarction in the left ventricle is hard to determine.[73] Figures vary, but on the whole seem to show that the incidence of anterior and posterior infarcts is about equal, possibly with some predominance of the anterior surface. Two sets of figures (Tables 9-10),

TABLE 9. SITES OF INFARCTION IN A SERIES OF 556 CASES[85]

Site	*Number of Cases*	
	Recent infarct	*Healed infarct*
Anterior	190	222
Posterior	109	122
Septal	5	5
Right ventricle	8	22
Anterior and posterior	45	62
Total	357	433

both of carefully studied cases, are representative.

Septal lesions alone are rare, but extensions

TABLE 10. SITES OF INFARCTION IN A SERIES OF 458 CASES[93]

Site	Number of cases
Anterior	179
Posterior	144
Anterior subendocardial	17
Posterior subendocardial	6
Posterolateral	17
Posteroseptal	19
Anterolateral	10
Extensive posterior and lateral	10
Anteroseptal	34
Septal	4
Unidentified	18

to the septum are common. Of the 190 cases with fresh anterior infarcts (Table 9), 72 showed extension into the adjacent septum; of the 109 fresh posterior infarcts, 35 extended into the septum. The size of the affected cardiac area ranged from 0.3 × 0.1 cm to 12 × 15 cm.

The lateral wall of the heart is involved more often than was formerly believed In a study of 106 cases, left lateral wall infarcts were found in 17 9 per cent; right lateral wall, in 0.9 per cent; posterobasal, in 25 5 per cent; anteroapical, in 54.9 per cent.[84] Somewhat lower figures are reported in other studies, for example, 5 left lateral lesions among 153 cases of infarction.[94]

FIBROSIS

Cardiac fibrosis may occur at the site of a healed infarct; it may also occur in the absence of infarction in chronic ischemia of the heart due to long-standing coronary narrowing While it is believed that complete tissue death and subsequent replacement by fibrotic tissue will not occur after less than 20 minutes of ischemia, it is not unlikely that repeated bouts of anoxemia in angina pectoris of long standing may lead to fibrous scarring of the myocardium which eventually results in myocardial weakness and failure Ischemia is not the only cause of cardiac fibrosis, for example, hyperplasia of the interstitial connective tissue is said to be invariably present in cardiac dilatation from whatever cause

The chemical composition of the myocardium may be affected by ischemia. The creatine content of infarcted areas is half that of uninfarcted areas. The same general rule applies to the creatine in the heart muscle as to other muscles: the highest content is found in the most active and efficient muscles. In the heart, the left ventricle, which is the more active part of the heart, contains 170 to 180 mg. creatine per 100 cc., as compared to 130 mg in the right ventricle, the less active part In congestive heart failure, these figures are reduced by about 30 per cent, in infarcted areas, the levels are still lower

REGENERATION

Comparatively little has been added to the literature on the regeneration of heart muscle since a review in 1912[29] There is little evidence to indicate the existence of regeneration Heller[33] believed that regeneration occurred, especially in toxic degeneration, and that the primary muscle bundles multiply by longitudinal division and splitting of nuclei.[85] Others have thought that the "muscle giant cells" found close to infarcted areas are an indication of regeneration Saphir and coworkers[71] suggested that these cells might not represent a regeneration attempt but result rather from a foreign body reaction, they found no giant cells, but did find apparent hypertrophy of muscle fibers in areas surrounding infarcts Karsner and Dwyer[36] saw no evidence of myocardial regeneration, the nuclear changes which were present they regarded as degenerative rather than mitotic. After critically examining the theory that the connective tissue found in myocardial infarction may be formed from muscles cells or "cells of muscle origin" as a result of anaplastic or retrogressive changes, they concluded that cicatrization of the infarct is due to proliferation of pre-existing connective tissue and blood vessels and is not materially different from cicatrization in other organs.

CHANGES IN CARDIAC SIZE

The size of the heart in coronary disease varies greatly. In a study of 113 cases, 45 of the hearts (40 per cent) weighed 400 Gm or less, even in the presence of advanced narrowing or obstruction of large arteries, in 12 of 24 cases of complete occlusion of one of

the main branches, the heart weight did not exceed 400 Gm.[55] In another series of 94 cases, 25 of the hearts did not weigh more than 400 Gm.[1] A roentgenographic study of the heart in 200 patients who had survived coronary thrombosis for at least 3 months revealed no definite enlargement in about one third of the cases after 3 years, despite the fact that occlusion had recurred in some of the patients.[58] Other investigators, too, have concluded that there is no relation between cardiac hypertrophy and coronary disease.[34, 47, 62]

On the other hand, certain clinical reports would seem to indicate the existence of such a relationship. Parkinson and Bedford[60] felt that the only factor producing cardiac enlargement may be infarction. Smith and Bartels[78] found hypertrophied hearts in most cases after coronary occlusion. In a series of 122 cases examined postmortem, no other cause for the enlarged hearts was apparent, and it was concluded that heart weight is a function of the degree of coronary sclerosis.[56] Some degree of hypertrophy has been found with increasing severity of the sclerosis, and a considerable increase in size when congestive heart failure supervenes.[19]

Animal experiments have added little to the clinical evidence. In one study, ligation of coronary arteries in dogs produced cardiac infarction, but after 319 days there was still no evidence of hypertrophy.[82] Another study reported hypertrophy after experimental ligation of canine coronary arteries.[77] Repeated injection of epinephrine resulted in enlargement of the heart.[81] Cardiac enlargement in arteriovenous aneurysm has been attributed to deficient myocardial nutrition.[44] It is well known that cardiac hypertrophy may be caused by anemia, this hypertrophy, however, may be due to the increased work which the heart must do.[37] Rabbits with coronary atherosclerosis due to a high cholesterol diet had significantly enlarged hearts, atherosclerosis of the aorta, systemic arterial hypertension, aortic valvular defects, myocardial inflammatory disease, and other effects of the diet could be excluded as factors in the production of the cardiac enlargement.[37] Although the possibility that the effect on the heart might be either a direct one, or an indirect one mediated by the endocrine glands could not be excluded, the conclusion was reached that the coronary atherosclerosis as such produced the hypertrophy and that ischemia played a role. Other workers from the same laboratory found that the cholesterol content of the myocardium was increased in these animals, but that this could not account for the increased weights of the heart.[85] They concluded that myocardial ischemia alone could be the sole cause of cardiac hypertrophy. Similar results have been reported in chicks.[15]

In a thorough clinical study of the subject, with an analysis of 1645 autopsies, the possibility was investigated that coronary sclerosis and its resultant ischemia, congestive failure, or myocardial damage, as evidenced by myocardial fibrosis, could produce cardiac enlargement.[49] All cases with hypertension were excluded. The conclusions reached in this study were: (1) there is a close correlation between coronary sclerosis and hypertension, and the latter usually explains any increase in heart weight. (2) There is no evidence that coronary sclerosis, heart failure, or myocardial fibrosis produces cardiac hypertrophy. This is substantially the same conclusion as that of Bell and Clawson,[5] who maintained that cardiac hypertrophy is not caused by coronary disease, and that it is more likely that coronary sclerosis occurring in the course of hypertension tends to prevent further cardiac hypertrophy. Every one who has written on the subject, including Maun, has reported cases of heart enlargement which could not be explained on the basis of hypertension or any of the other commonly accepted causes.

From a review of the literature, and from my own experience, I am led to believe that an enlarged heart may occur in some cases of coronary disease in the absence of hypertension, valvular disease, or heart failure. In most cases, significant or repeated failure will result in enlargement, although occasionally, despite several intensive episodes of cardiac failure the heart at autopsy was found to be small. In 1 case of advanced involvement of the coronary arteries with myocardial fibrosis, and heart failure for 3 months, the heart weighed only 325 Gm.

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CHAPTER 7

Angina Pectoris

THE HISTORY of coronary artery disease started almost full grown with the account by Heberden of its most spectacular symptom, angina pectoris. His report is a masterpiece of clarity and completeness, and little has been added since to improve the clinical description.

The typical case of angina pectoris presents a picture so characteristic that it can hardly be confused with any other syndrome.[23a] The features of such a case are: (*1*) pain which is primarily substernal or precordial; (*2*) radiating pain to the left shoulder or arm, (*3*) pain brought on during or immediately after exertion, emotion, or chilling; and (*4*) quick relief by rest or nitroglycerin Any patient who complains of pain with these four features has both the symptom (angina pectoris) and heart disease, atheroma of main coronary arteries, in the vast majority of cases Atypical symptoms often plague the physician, but the common forms of angina are identified without trouble

MAIN CHARACTERISTICS

LOCATION OF DOMINANT PAIN

The first and most bitter complaint is of substernal or precordial pain An accurate diagnosis becomes difficult only when the dominant pain is felt in some other location, or the radiating pain takes precedence in the patient's awareness over the chest pain, or the pain is minimal or does not occur. In over half the cases the pain is substernal,[11] and in most of the rest it is just to the left of the sternum in the precordial area. Rarely is the dominant pain farther to the left; although it may spread as far as the apex or the left costal margin, it is almost never felt there principally. Except in the rarest cases, the pain is not exclusively abdominal, it may, however, extend to the abdomen In patients complaining of abdominal pain it will as a rule actually be subxiphoid or at least have some supradiaphragmatic component, even though the severest pain is not felt in the thorax. Pain is never felt at or below the umbilicus, except as an atypical radiation

RADIATION OF PAIN (Fig. 30)

The typical radiation is to the left shoulder and arm, possibly extending to the fingers The area of radiation after it has reached the arm is almost invariably on the ventral surface, narrowing at the wrist so that it is usually limited to the ventral surface of the little finger. The pain may extend in a continuous band from the precordium up to the shoulder and down the arm, or with a gap so that two separate areas of pain may be distinguished

The left side of the neck and the left side of the face (*e g*, teeth or ear) are the next most common areas to which pain radiates Less common still is pain radiating to the left scapular area, the right arm, or both shoulders and both arms, such pain radiation is an added source of confusion when the clinical picture is not clear Even rarer sites are the midback and the lower abdomen Radiated pain is sometimes felt in the upper abdomen, especially in the right upper quadrant in the presence of gallbladder disease. This is an example of the predilection of pain to radiate to areas affected by other diseases

The undeviating, individual pattern of pain radiation is its most characteristic feature Any gradual or sudden change in the pattern is an indication that further cardiac changes, usually increasing coronary narrowing, have taken place

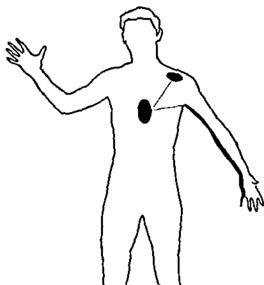


FIG 30 Radiation of anginal pain. (Top) Typical radiation (Bottom) Atypical sites of radiation, front and back (Adapted from Pfizer "Spectrum" in the J A M A, May 29, 1954)

The referred pain is in some cases the most annoying symptom in angina pectoris and the one which brings the patient to the doctor. In such cases, however, skillful questioning will disclose the presence of thoracic pain as well. The middle-aged patient whose chief complaint is pain in the left shoulder or arm must therefore be questioned closely Rarely, there may be no thoracic component, the only pain felt being in the area of radiation; sooner or later, however, pain in the chest almost invariably appears. Diagnosis in such cases calls for special alertness

CHARACTER OF PAIN

In describing the thoracic component of their anginal pain, patients most often use the adjective, *constricting*, or some such synonym as *squeezing*, *tight*, *cramping*, *heavy*, or *pressing* The pain is less often described as *burn-*

ing, boring, stretching, aching, viselike, or *choking.* The word "pain" is more often used by the doctor than by the patient, who often prefers the term "pressure." An outstanding feature is the pain's vague location and character. In true angina pectoris, the patient finds it much more difficult to describe his symptoms accurately than in neurotic or noncardiac anginal pain. Seldom is the pain sharp, when the patient uses this word he generally means that it is severe rather than lancinating or pricking. The term *aching,* as used by patients, more usually applies to the radiated pain. The patient may not use the word pain at all, but complain of a disagreeable sensation or of smothering, the wary diagnostician will not fall into the pitfall of not recognizing this complaint as one of anginal pain

In one series, 40.2 per cent of the patients described the chest pain as constricting, 32.5 per cent could not find a descriptive term; 9 5 per cent said the pain was aching, 1 3 per cent complained of "numbness," and 1.3 per cent felt sharp or lancinating pain [11] In another series, 61 per cent of the patients complained of pressure and heaviness; 42 per cent, of constrictive, squeezing, strangling, compressing, or viselike pain; 41 per cent, of aching, dull, gnawing, throbbing pain or discomfort; 32 per cent, of tightness, 14 per cent, of choking, 13 per cent, of sticking or knifelike pain, and 10 per cent, of burning pain [22] In my own series of 500 cases of unequivocal angina pectoris, 70 per cent used the term "pressure" or some equivalent word to describe their symptoms, and an additional 18 per cent used such a term on close questioning.

Other characteristics are somewhat less important Onset or relief of the pain is seldom *extremely sudden As a rule, the pain builds* up gradually and usually lasts a minute or two. When a shorter duration (a few seconds) is described, the patient has probably underestimated the time considerably. On the other hand, rarely does the pain last more than a few minutes, and almost never as long as half an hour If it does, fresh coronary narrowing or muscle infarction must be suspected. The pain of true angina pectoris appears coincidentally with or immediately after the precipitating factor The amount of effort or exertion which will produce pain may vary from day to day and from hour to hour.

Certain negative characteristics are useful in diagnosis. The pain is seldom sharp or lancinating, rarely throbbing or synchronous with the heart beat, and not often of extreme intensity although it may be accompanied by angor mortis or a sense of impending dissolution The disagreeable sensations aroused by the pain are out of proportion to its intensity, probably due to reflexes to the skin with resultant vasoconstriction and reflexes to the gastrointestinal tract which reduce tonus and produce a sinking feeling in the epigastrium.

The pain of angina pectoris is not made worse by breathing. "The pain which bears a direct relationship to breathing, coughing, laughing, yawning or other respiratory acts, is in all probability not angina pectoris "[11] Pain consistently induced by one motion, such as bending or squatting, is not a sign of angina pectoris. Changes in body position, with the exception of recumbency, do not induce or relieve the pain of angina pectoris.

Anginal pain is precipitated more easily after meals and in the presence of "abdominal distention." In either case, belching or loosening a tight belt may bring relief, this may be a cause of some difficulty in differentiating angina from gastric disorders Constipation does not affect angina, but the act of defecation, especially if it requires much breath holding or squeezing, may cause anginal pain. In some cases, ingestion of food has been reported to prevent anginal pain,[11] hypoglycemia may have been a contributing factor in the pain of these patients. Dysphagia does not accompany angina except in the presence of definite cardiac enlargement.

Palpitation accompanying chest pain is a rare complaint, except in the neurotic patient. *On the other hand,* ectopic beats may result in heart consciousness and be interpreted by the patient as pain In an occasional case, paroxysmal tachycardia may induce angina pectoris, especially in the presence of coronary disease, the history will then show that the palpitation preceded the onset of pain. Hyperthyroidism, which increases cardiac work, is often accompanied by palpitation and increases susceptibility to anginal pain. Other conditions which must be considered when the patient complains of both angina and palpitation are hypoglycemia and intermittent hyperadrenalemia

RELIEF

The angina of exertion is usually relieved quickly by rest. Nitroglycerin or amyl nitrite promptly relieves most attacks of anginal pain, whatever the cause may be, as a corollary, chest pain not influenced by nitroglycerin is not due to angina pectoris. In patients in whom nitroglycerin no longer is effective or in whom much larger doses than usual become necessary for relief, further cardiac damage (coronary occlusion or myocardial necrosis) should be suspected Patients in whom recumbency brings on anginal pain often obtain relief by sitting up.

SYMPTOMS OTHER THAN PAIN

These may be present during or immediately after an attack Singly or in any combination, there may be sweating, weakness, tremor, fainting, collapse, vertigo, and dyspnea Nausea or vomiting are rare, except when the attack is prolonged or infarction is in the offing, these symptoms can be explained by the reflex changes in intestinal tonus produced by coronary insufficiency Any of these symptoms may replace thoracic pain, in part or completely, especially in patients with a high pain threshold But even in such patients there will be some pain in the thorax or in an area of radiation or pain will soon appear in the clinical picture

Painless angina (angina sine dolore) is rarer than painless infarction. This rarity may possibly be ascribed to the difficulty of diagnosis in the absence of typical pain or radiation of pain

The patient with anginal pain is often highly suggestible. In his eagerness to be helped, he attributes any subjective improvement to the last therapy tried It is erroneous to assume that pain in organic disease, whether it is angina, ulcer, or cancer, is not alleviated by suggestion Any regimen prescribed with an air of confidence by a cheerful and persuasive advisor is usually helpful for a time

In a patient whose personal life is in good order, anginal attacks are fewer and less severe, whereas adversity and emotional stress have the opposite effect. Pleasurable activity is much less likely to bring on an attack than other, equally strenuous but less pleasant exertions. Thus the patient less frequently reports distress from a walk to the theater than from walking to work

RECUMBENCY AND ANGINA

Activity in the recumbent position is usually less distressing than in the upright position. For example, coitus induces angina far less often than does walking, despite a greater increase in heart rate. A severe form of angina pectoris (angina decubitus) is brought on merely by lying down. But not all angina suffered at night occurs as the result of the recumbent position; the pain may be an angina of effort or due to some other cause —spontaneous hypoglycemia, paroxysmal tachycardia, chilling, nocturnal dyspnea, or nightmares I have found the last to be a frequent cause of angina pectoris or paroxysmal dyspnea. Disturbing dreams may raise the systolic pressure as much as 70 mm , and may cause an increase in heart beat of more than 20 beats per minute [20] Psychotherapy may be necessary to alleviate the terrifying symptoms which are sometimes brought on by nightmares.

ANGINA DECUBITUS

This is a severe form of angina pectoris brought on by the recumbent position. It eventually develops in many patients with typical angina pectoris The time from first onset of angina to the death of the patient is not significantly different whether angina decubitus develops or not, but once angina decubitus sets in, the prognosis is poor, the duration of life being reported as only 2 8 years [32] It is a safe assumption that angina decubitus is a sign of advanced coronary disease.While the cause of angina decubitus is not clear, the reduction in blood pressure which accompanies the recumbent position may be partly responsible. In the presence of advanced coronary sclerosis, coronary flow is at best just above a critical level, so that depression of flow below this level results in ischemic pain.

DIAGNOSIS

HISTORY

An accurate history is most important in correct diagnosis A definite diagnosis of angina pectoris can be made if the history discloses the four complaints listed at the beginning of this chapter. The patient may

have any number of neurotic manifestations in addition, but the diagnosis, if made on the basis of this history, is safe and unlikely to be overthrown

The diagnosis becomes difficult only in those cases in which one or more of the characteristic symptoms are absent or there are atypical symptoms For example, the patient may describe the pain as knifelike, or the pain may be referred to the back or the abdomen instead of to the left shoulder or arm. Corroborative evidence of cardiovascular disease or of coronary insufficiency is important in such cases. The former suffices if the history is strongly suggestive of angina, the latter is desirable for a clear-cut diagnosis and is essential in completely atypical cases An illuminating comparison of the manifestations of chest pain in true angina pectoris and in "functional" states is summarized in Table 11, adapted from a report of Master and associates[33] It is noteworthy that some of the patients with true angina had atypical manifestations while some patients with functional disorders reported a few symptoms of coronary disease. Border-line cases may create diagnostic uncertainty, but a careful history and the use of various diagnostic aids will in most cases establish the diagnosis without too much difficulty.

TABLE 11 CHEST PAIN IN 100 CASES EACH OF CORONARY DISEASE AND FUNCTIONAL DISTURBANCES

Pain	Coronary disease	Functional disturbances
Type		
Constricting	42	17
Sticking	13	14
Aching	41	45
Pressure	61	52
Location		
Substernal	41	23
Precordial	30	44
Chest		
Entire	22	13
Left	19	29
Right	1	1
Back	8	4
Epigastrium	4	1
Onset		
Effort	91	34
Emotion	53	25
Spontaneous	31	66
Meals	25	10
Cold	23	3
Coitus	13	2

CARDIOVASCULAR DISEASE

Any evidence of cardiovascular disease is of positive value, and the diagnosis of angina becomes more definite as any condition such as hypertension, which increases the susceptibility to atheroma, is encountered In addition, all the factors which play a role in the pathogenesis of coronary disease, such as age or sex, must be evaluated, although they may be of small help in any given case Any physical sign pointing to the vessels, such as cardiac enlargement, significant murmurs, diminished pulse in the lower extremities, or retinal changes, is significant, as is intermittent claudication of the legs

SIGNS OF CORONARY INSUFFICIENCY

The presence in the immediate family of coronary disease, early or sudden death, angina pectoris, hypertension, diabetes mellitus, xanthomatosis, or hypercholesterolemia makes the diagnosis of angina pectoris more likely but is not conclusive evidence for such a diagnosis

The patient must be thoroughly examined for the possible presence of diabetes mellitus, myxedema, hypertension, xanthomatosis, or any other condition associated with a high blood cholesterol level Among the conditions which impair the quality of the blood reaching the myocardium, anemia is the most likely disease to produce angina Hypoglycemia and chronic anoxia have to be ruled out. Of the conditions which increase cardiac work, hyperthyroidism and paroxysmal hypertension due to adrenal tumor are the most important

The electrocardiogram may give evidence of recent or old myocardial infarction, when this is combined with a suggestive history, the diagnosis of angina is practically certain. Nonspecific electrocardiographic changes, indicating bundle branch block, intraventricular block, or conduction defects, or changes in the main or T wave complexes, which point to cardiac damage, indicate, in the absence of rheumatic or syphilitic disease, coronary narrowing with resulting myocardial

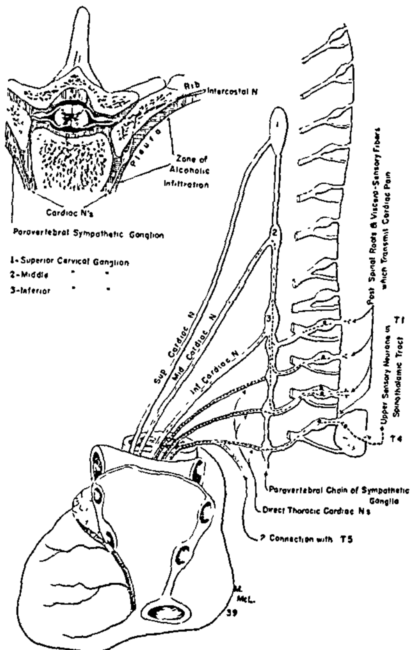


FIG 31 Sensory nerves of the heart (From White and Smithwick The Autonomic Nervous System, 2nd ed, 1941 Courtesy of the Macmillan Co)

scarring, at least in older patients If the tracing shows the pattern of ventricular strain, cardiac hypertrophy or hypertension may be present. If the electrocardiogram is normal or the changes are not specific for damage associated with coronary cardiac disease, further efforts to find electrocardiographic evidence of coronary insufficiency should be made (*see* Chapter 10). Even in the presence of established past myocardial infarction, it may be advisable to ascertain whether the patient's complaints are truly of anginal origin

PAIN PATHWAYS FROM THE HEART

It is highly probable that pain sensations travel the same path from the heart to the central nervous system whether the pain is caused

by transient angina or by myocardial infarction (*see* Fig 31)

Sensory axons from the cardiac plexuses run along the middle and inferior cardiac nerves and over the upper three thoracic rami Apparently, painful stimuli are not transmitted along the superior cardiac nerve and the superior cervical ganglion, nor are they conducted along thoracic rami lower than the third dorsal segment

Stimuli conducted along the middle and inferior cardiac nerves are carried back to the first thoracic segment, all afferent painful sensations must therefore pass through the first three thoracic segments, which act as a bottleneck. This of course simplifies the neurosurgical procedures involving severance of the afferent pathways. The distribution of the cardiac sensory nerves is strictly unilateral, interruption of the nerves on one side may not eliminate the pain felt on the other side of the midline.

Anatomically and physiologically, the cardiac afferent nerves are not, strictly speaking, part of the autonomic nervous system, they are, in fact, displaced somatic neurons By definition, the autonomic nervous system is only concerned with glandular secretion, smooth muscle, and visceral activity. The nerves to the heart, however, are mixed nerves which carry sympathetic motor and somatic pain fibers; the latter have their cells of origin in the posterior root ganglions, their central processes enter the posterior horn of gray matter, and the peripheral portion runs in continuity through the paravertebral ganglions and cardiac nerves to the heart[32]

CAUSES OF CARDIAC PAIN IN CORONARY DISEASE

The relationship between angina and coronary artery disease was recognized almost immediately after Heberden first described angina pectoris.[6] Classic angina pectoris is practically always the result of heart disease —in well over 90 per cent of the cases, coronary artery disease, and of valvular disorders in most of the remainder But the obverse does not follow; while angina is the most dramatic and the most frequent symptom of coronary disease, it occurs in far fewer than 90 per cent of patients. In view of the frequency with which coronary occlusion or myocardial infarction is found at autopsy, it is evident that angina pectoris of the classic variety or of sufficient severity to bring the patient to a physician occurs in less than half or even a third of all cases of coronary disease

There is little correlation between the severity of heart damage and the pain which the patient suffers Small lesions may produce intractable angina; on the other hand, extensive infarction and scarring of the heart is often painless In most such cases, differences in collateral circulation account for the variation in subjective reactions, the currently held theory of transient coronary insufficiency therefore satisfactorily explains most cases of anginal pain (*see* Chapter 1) Intermittent ischemia or, possibly, anoxia causes cardiac pain, probably through intermediate chemical changes

But this theory fails to explain every case of anginal pain, especially those cases in which the pain is completely disproportionate to the morbid cardiac changes[4] It seems reasonable, therefore, to fall back for an explanation on varying pain susceptibility in this, as in all visceral, pain Some individuals, with a high pain threshold (whatever the reason for it may be) will feel little or no anginal distress; others, who are hypersensitive to pain, will suffer early and severely from angina In any event, no attempt should be made to correlate closely the patient's complaints and the extent of disease. Angina is often compatible with long life

The three possible sites for the origin of anginal pain are the aorta, the coronary arteries, and the myocardium. All of these tissues seem to have sensory nerve terminals, so that theoretically they can be the sites for the origin of pain

The aorta as the site of pain has been proposed, since numerous fibers ascend from the aorta to the cardiac ganglions and then take the same route through the upper thoracic sympathetic ganglions as do fibers from the heart itself The aortic origin of some cardiac pain therefore cannot be excluded However, on the basis of experimental and postmortem studies, it may be safely concluded that cardiac pain can be

produced in the heart itself, and that in most cases of typical angina pectoris and myocardial infarction it has such an origin

Another source of cardiac pain was believed to be the mechanical action of disease processes. While the presence of a thrombus, as such, does not cause pain by distending the arterial lumen, it was thought that a sudden increase in coronary pressure proximal to the obstruction might produce the pain. This theory however, is based on an erroneous physical concept and may be abandoned[34]

Although vascular spasm might possibly stimulate sensory nerve endings and thus cause pain, it is unlikely, since the coronary branches contain insufficient muscle fiber for such intense spasm to be probable Of course, this does not exclude the possibility that coronary spasm may induce relative cardiac ischemia and anginal pain

In an experimental study, pain was produced in dogs by causing tension on the walls of coronary vessels without so affecting coronary flow as to produce electrocardiographic changes[21] Presumably, the pain in this experiment was not mediated by any chemical stimulus The investigators maintained that proponents of the "ischemic theory" had not demonstrated experimentally that pain can be *produced by a chemical stimulus in the absence* of any mechanical factor

The most widely held theory now is that ischemia produces the cardiac pain There is every reason to believe that ischemia *occurs during* all or most attacks of angina pectoris Two possible mechanisms have been proposed to explain the production of pain by ischemia. (*1*) lack of oxygen or oxygen debt, and (*2*) irritating metabolites (P factor) formed by contracting muscle.[15]

In some patients, breathing low-oxygen mixtures (as in Levy's anoxemia test) will cause cardiac pain However, as has been demonstrated,[15] the oxygen in inspired air may be depleted to the point of producing electrocardiographic changes without causing pain in patients with known angina pectoris. Conversely, anginal pain is often produced in the anoxemia test without corresponding [illegible]

This substance, whatever it is, may also be formed by resting muscle, but much more slowly than by an actively contracting one. While anoxemia probably does not play a dominant role in the formation of P factor, it probably accelerates such formation. The P factor seems to be acid in character and to be closely related to the lactic or phosphoric acids formed during muscular catabolism. After experimental coronary ligation, it forms rapidly in the heart at the expense of glycogen. In man, the factor is probably neither potassium nor lactic acid, since neither is increased with muscular ischemia.

Whatever the nature of the chemical agent may be, it seems likely that most cardiac pain is caused by chemical irritation—probably by products of anerobic metabolism—of sensitive tissue

Transient ischemia of nerves resulting from reflex spasm of the vasa nervorum has been suggested as a mechanism, or at least as an additional mechanism, in cardiac pain and especially in referred pain[27] Ligation of a coronary artery causes the vasa nervorum in the left upper extremity of animals to contract The importance of this finding in connection with disease in man remains to be evaluated

It has been persuasively proposed that an *anginal attack on effort or emotional stress is* the result of an acute influx of norepinephrine and epinephrine into the myocardium[25] These catechol amines induce excessive local oxygen consumption and hypoxia regardless of the degree of cardiac work, if the coronary arteries are sclerotic and cannot dilate, the hypoxia will exceed the pain threshold.

DISEASE PROCESSES CAUSING ANGINAL PAIN

Since angina pectoris of the classic variety is almost invariably the result of transient coronary insufficiency, anything which reduces the flow or its effectiveness or increases the metabolic demands of the heart may result in angina, especially in the presence of atheromatosis.

ANEMIA As first observed by Herrick and Nuzum,[12] anginal pain occurs frequently *in all types of anemia, especially in patients* with some degree of coronary disease.[24] Although total coronary flow is increased in

anemia, there is nevertheless a relative coronary insufficiency, for the blood is deficient in oxygen and other nutrients. The following case histories are illustrative.

Case 1. A man of 60 suffered pain in the precordium and left shoulder on the slightest exertion. The electrocardiogram showed left bundle branch block. He had pernicious anemia, with an erythrocyte count of less than 1,000,000 After treatment, the blood count returned to normal and anginal pain occurred only after strenuous effort, but the electrocardiogram remained unchanged.

Case 2: A 55 year old man with peptic ulcer suffered several episodes of gastric hemorrhage There was no hematemesis Each bout of hemorrhage was ushered in by an attack of anginal pain The electrocardiogram clearly indicated the presence of organic coronary disease

Case 3: A 34 year old man with a hiatus hernia and gastric bleeding was first seen in delirium; his erythrocyte count was below 500,000 He had suffered from angina pectoris for some months and had been under the care of a cardiologist. The electrocardiogram showed a flattening of the T waves in all leads, with a slight inversion in lead I. The angina disappeared and the electrocardiogram reverted to normal as soon as the anemia was corrected During a 5 year follow-up, no evidence of coronary disease was found

VALVULAR HEART DISEASE AND PULMONARY HYPERTENSION

Cardiac pain is occasionally a vexing problem in chronic valvular disease, even when there is no gross cardiac enlargement to produce diffuse aching pain Chronic endocarditis, as such, usually causes atypical pain, but sometimes the pain may be the classic angina of effort Nothnagel[23] seems to have been the first to report cardiac pain in valvular heart disease; he noted pain in 18 per cent of his patients with mitral stenosis; in some of the patients, there was an associated angina pectoris. In a series of 741 patients reported by Levine and Kauvar,[16] 2 6 per cent had angina, the average age at onset was over 50 years Postmortem examination of 16 of these patients showed that in 3 the coronary arteries were normal. Stuckey has reviewed the literature and has added 34 cases of effort angina in mitral stenosis (8 5 per cent of a series of 400 patients); the stenotic lesion in all 34 patients was classified as severe. Pain is not a feature of mitral insufficiency.

Precordial pain has been noted in aortic insufficiency.[5, 33] This lesion is often found in association with mitral stenosis, but chest pain may undoubtedly occur in young individuals with aortic insufficiency but without mitral or coronary lesions Operative procedures which relieve the insufficiency do, in fact, alleviate this pain [14] In a carefully studied series of 100 patients with aortic insufficiency, angina pectoris was noted in 50 per cent, regardless of the age of the patient In none of the cases studied at autopsy were organic changes in the arteries found. The observers offer the following possible explanations for the cardiac pain decrease in coronary flow because of the lower diastolic blood pressure; "sucking" action of the regurgitant stream on the coronary arteries, the Bernoulli principle, and relative coronary insufficiency related to the large left ventricular mass [27a]

Aortic stenosis is not infrequently associated with precordial pain, either in the form of a rather severe ache unrelated to exercise or with all the attributes of angina pectoris Aortic stenosis also resembles coronary disease in its tendency to cause sudden death A reduced systolic volume flow has been found in this condition, resulting in a reduction of coronary minute flow [10] Aortic stenosis, which unlike aortic insufficiency is found in the older age groups with possible coronary narrowing, is no doubt an aggravating factor in cardiac pain Two mechanisms play a role in this cause of pain. (*1*) the hypertrophied left ventricle, which may have a reduced blood supply due to coronary narrowing, must perform increased work, and (*2*) a diminished cardiac output. Calcareous aortic stenosis, there is some reason to believe, occurs more often in persons with an elevated blood cholesterol level.[2] Anginal pain has been reported to occur in 28 per cent of patients with aortic stenosis, whether the condition is congenital or acquired [13]

In a series of 448 consecutive cases of congenital heart disease, anginal pain was a complaint in 4 8 per cent 6 of 26 patients with aortic stenosis, 6 of 38 patients with severe pulmonary stenosis, and 6 of 30 patients with pulmonary hypertension.[25] All of these patients had two features in common

an obstruction to the blood circulation and evidence of a low cardiac output, both clinically and by catheterization

Results of exercise tolerance tests are often positive in the angina associated with valvular disease. Nitroglycerin does not prevent the changes,[28] so that coronary artery narrowing does not account for the coronary insufficiency It is noteworthy that coronary sinus catheterization and the nitrous oxide technic of Kety and Schmidt performed in 6 patients with advanced mitral stenosis revealed the coronary blood flow to be significantly reduced [28]

Pulmonary hypertension is a major feature in many of the patients under discussion here and may be an important factor in producing pain. *Pulmonary hypertension angina* (*angine pulmonaire hypercyanotique*) was a *term first used by Vaquez and Giroux* [29] Many such cases have since been reported For example, 3 of 6 patients with idiopathic pulmonary hypertension had angina,[35] 6 patients with pulmonary hypertension of varied etiology had chest pain identical in character with true angina which was not relieved by nitroglycerin and of longer duration [30] The pain in the latter group was often accompanied by dyspnea and was relieved by oxygen or aminophylline The reason for the pain in *pulmonary hypertension is not established*, myocardial anoxia, low cardiac output with cardiac ischemia, and distention of the pulmonary arteries have all been suggested

COLD

The induction of anginal pain by cold is striking. Cold bed sheets and cold drinks or wind are a common precipitant of angina, and pain is induced by slighter physical effort in cold weather than in mild. T wave inver*sion has been found after* drinking iced water;[35] 2 cases of myocardial infarction immediately following the drinking of cold water have been reported [19] In a study of this phenomenon it was found that the exercise tolerance of patients with angina pectoris was decreased in a cold room or if the patient held an ice cube in a warm room (analogous to being warmly dressed in cold weather but with the face exposed); cardiac work or output was not increased, and it was concluded that the effect of cold is probably the result of a reflex—either vasoconstriction or the prevention of vasodilatation, which may affect the nonrigid collateral vessels rather than the fairly rigid main arteries.[7] In a study using a standard test consisting of the application of an ice cube to various parts of the body for 2 to 15 minutes, 3 of 20 patients with angina showed electrocardiographic *changes, some normal subjects had transient* T wave depression; sites especially sensitive were the anterior forearms, the nose, the nipple area, and the abdomen.[1] This suggests that chilling of the nose may be as important in inducing pain as the breathing of cold air Occasionally, the reactions to the test were delayed, and the effects seemed to be accentuated after meals.

EXTRACARDIAC PAIN

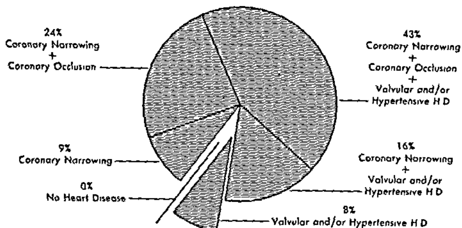
In susceptible patients pain elsewhere in the body alters the T waves of the electrocardiogram and may induce angina [9] Pressure on an area to which pain is usually referred or on a sensitive area of the skin, subcutaneous tissue, or muscle may precipitate an anginal seizure.

ECTOPIC RHYTHMS

Tachycardia, whatever its cause, may result in coronary insufficiency, especially if *the rate is over 150 Paroxysmal tachycardia* often causes cardiac pain. Angina, too, is sometimes associated with ectopic beats. In a review of the literature, it was pointed out that quinidine or procaine amide (Pronestyl) may give relief.[3] It is a matter of conjecture which is more important—cardiac ischemia producing irregularity or irregularities in rhythm causing ischemia.

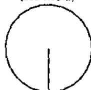
In the vast majority of cases, angina pectoris is the result of coronary disease. In the remainder, there is almost always some sort of heart disease. It may be safely assumed therefore that the patient with typical angina pectoris without evidence of other organic heart lesions has coronary narrowing with intermittent ischemia (Fig 32).

FIG 32 (Facing page) The etiology of angina pectoris. A, as found in 130 cases; B, coronary artery disease and angina pectoris; C, coronary occlusion and angina pectoris (Courtesy of Dr H. L. Blumgart)



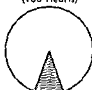
A

Normal Coronary Arteries (225 Hearts)



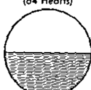
0% Angina

Narrowed Coronary Arteries (100 Hearts)



11% Angina

Occluded Coronary Arteries (64 Hearts)



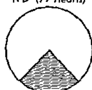
50% Angina

Normal Coronary Arteries Hypertensive and/or Valvular H D (102 Hearts)



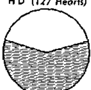
10% Angina

Narrowed Coronary Arteries Hypertensive and/or Valvular H D (79 Hearts)



24% Angina

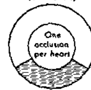
Occluded Coronary Arteries Hypertensive and/or Valvular H D (127 Hearts)



59% Angina

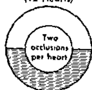
B

Coronary Artery Disease (27 Hearts)



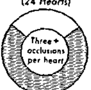
33% Angina

Coronary Artery Disease (12 Hearts)



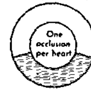
50% Angina

Coronary Artery Disease (24 Hearts)



71% Angina

Coronary Artery Disease Hypertensive and/or Valvular H D (39 Hearts)



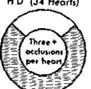
41% Angina

Coronary Artery Disease Hypertensive and/or Valvular H D (23 Hearts)



65% Angina

Coronary Artery Disease Hypertensive and/or Valvular H D (34 Hearts)



73% Angina

C

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CHAPTER 8

Myocardial Infarction

MOST PHYSICIANS are familiar by now with the clinical picture of major infarction. Nevertheless, even the most alert clinician may fail to diagnose this condition Frequently the pathologist finds an infarction on postmortem examination of a patient who has died, or who seems to have died, of other causes. No doubt, as diagnostic methods are perfected, this situation will be less common.

Infarction is often found incidentally during examination for other conditions, but some cases are overlooked because they do not conform to the classic picture. Understandably enough, less severe grades of cardiac infarction (minor infarction) are missed even more often A clearer concept of major infarction would lead to more accurate diagnoses of both major and minor infarcts

PRODROMAL SYMPTOMS

The pain of myocardial infarction may come on with startling suddenness As late as 1946, Cassidy[19] stated: "It is quite common for coronary disease to be entirely latent until sudden death occurs" But we now know that infarction is more commonly the end result of cardiac changes which produce symptoms and signs, at times quite obvious and sometimes so slight as to be easily overlooked. It is decidedly uncommon to have no warning of infarction The great or small omens are (*1*) those which have persisted for some time, and (2) those which immediately precede the acute episode by a period of a few hours to 3 weeks, at the most

The symptoms of long duration are very frequent; they may point directly to the coronary arteries—previous infarction, angina pectoris, etc.—or they may implicate the heart in a general way, for example, increasing breathlessness on exertion, which should suggest the likelihood of coronary disease These symptoms, however, may not be serious enough to make the patient seek medical advice; a sense of precordial oppression on exertion or excitement may be slight or not too troublesome, or the symptoms may be referred to other sites. Thus, for example, epigastric distress may be present for months before an acute occlusion Annual examination of any person over the age of 30 should therefore include careful electrocardiography, a chest roentgenogram, and a scrupulous evaluation of all symptoms, this would reduce the incidence of sudden and unexpected cardiac deaths to a very small number, although some "sudden" deaths, especially in the younger age groups, will always be encountered

In a fairly large number of patients, the symptoms precede an acute infarction by an interval of not more than 3 weeks The figures range from 9 3 per cent to 100 per cent[19, 23, 35, 80, 84, 100, 110] Of 139 carefully studied cases, 29 per cent gave a history of preceding prodromal symptoms of 3 months' duration at the most[64]

The typical, agonizing pain of infarction is preceded by precordial pain of varying nature, severity, and duration which then abruptly changes its character Many patients, with or without pre-existing angina pectoris, may suffer for weeks from a dull precordial pain of longer duration than that of angina, of untypical distribution, and not promptly relieved by rest, but more often, this period lasts only 6 to 48 hours I have noted prodromal symptoms in at least 50 per cent of my patients, usually within 2 days of the final, crushing blow The pain may radiate, although less frequently than in angina, to the neck, back, or upper extremity, and may even over-

shadow or replace the precordial pain The radiated pain is more likely to be of a burning or aching character, rather than the crushing *pain of infarction*[1] *Rest and mild* anodynes, such as aspirin or codeine, afford some relief from the pain which, however, is often transient in any case.

The pathologic changes which precede complete occlusion of a large vessel may take the form of (*1*) hemorrhage into a sclerotic plaque, (*2*) rupture of an atheromatous abscess, (*3*) incomplete thrombosis, (*4*) *coronary artery spasm,* (*5*) *gradual increase* in size of an atheroma, or (*6*) edema of the atheromatous plaque Coronary insufficiency results of course in pain, but it is just as prob*able that the prodromal pain may be caused* by a small infarct which expands until larger areas are compromised.

If prodromal symptoms were recognized, measures could perhaps be taken to prevent *a major infarction or minimize its results* Anticoagulant therapy, rest, and other properly applied methods at this point might avert disaster Obviously, despite all preventive measures, a large vessel will sometimes become completely occluded before sufficient collateral circulation can be established.

CLINICAL FEATURES OF MAJOR MYOCARDIAL INFARCTION

The classic case of myocardial infarction presents the following features. (*1*) The patient is a middle-aged man who has had some warning symptoms of heart disease (*2*) Following a variable, but short, period during which the pain gradually grows more intense and other symptoms increase, a stage of marked distress is reached, the pain is usually severe, and the patient frequently has a feeling of impending death. (*3*) The only effective remedy for the pain may be large, frequently repeated *doses of morphine.* (*4*) The patient is restless and anxious, in contrast to the rigidity and immobility of a patient during an attack of angina pectoris; his face is ashen gray; perspiration is profuse; the extremities are cold and clammy. (*5*) Nausea and vomiting are common. (*6*) The blood pressure may be normal or high at first, but as a rule drops sharply within a few hours, the pulse is generally high; cyanosis and dyspnea are often marked. (*7*) The rectal temperature rises within a few hours, and *may reach 103° F.* or higher. (*8*) The sedimentation rate and the leukocyte count increase. (*9*) The intensity of the first sound at the apex is in general definitely diminished, and a friction rub or some irregularity may be heard

PAIN

The causes of cardiac pain are discussed in Chapter 7.

CHARACTER The adjectives used by the patient to describe the pain of infarction are: *crushing, constricting, viselike, pressing, burning, sharp* is seldom used. Occasionally, the patient may be unable to describe it accurately, and will only say that it is extreme and agonizing One characteristic of the pain *has been suggested*[95] *as useful in the diagnosis* and prognosis of an acute infarction: the pain is typically intermittent, severe pain being followed by brief periods of comparative relief, succeeded in turn by renewed paroxysms of pain If the paroxysms become increasingly intense, and the periods of remission fewer and of shorter duration, the immediate prognosis is poor, conversely, if the remissions grow longer, the patient usually recovers. Steincrohn[95] described this syndrome picturesquely as "labor pains of the heart," and compared them to closely repeated attacks of angina pectoris These observations have been noted by us too

When the area of infarction is small, the pain may not be severe, and it is these cases which may be overlooked Cardiac pain, even when transient and atypical, should always arouse the suspicion of infarction, especially in a patient with known coronary disease or any of its precursors

LOCATION AND RADIATION The location and radiation of pain are about the same as in angina pectoris. Predominantly, the pain of a major myocardial infarction is in the anterior chest. As a rule it is rather diffuse, but the patient usually *points to the* sternum as the site of the pain, so that it may best be described as substernal; pain largely to the left of the sternum, which may be

described as precordial, occurs somewhat less often, pain dominantly in the apical or nipple area is rare. Total absence of pain in the anterior chest is unusual, and close questioning will generally reveal the presence of some pain in the chest. In exceptional cases, pain may be felt only in the left arm or shoulder; rarely, the pain may be only abdominal—in 16 of 240 cases in one series,[8] and in 1 reported case, the only manifestation was rectal tenesmus [63]

Radiation of pain (*see* Fig. 32) is common —in one series, in 67 per cent of the cases,[109] in another, in three fourths of the patients (83 per cent of those who survived and 57 per cent of those who died).[11] Most commonly, the pain is referred to the left arm or shoulder; often pain is felt in the epigastrium, or the right upper abdominal quadrant. Rarely, pain may radiate to the back; in 3 of 66 cases pain was felt in the cervical or lumbar vertebrae.[90] Bizarre radiation has been reported, as in 1 case in which the patient "nearly had his mastoid process opened for coronary thrombosis."[55] In a recent report, Sigler[63] wrote:

> Radiation of pain was most frequent to the various parts of the upper extremities and to the back of the chest. Next most frequent areas of radiation were the epigastrium and abdomen, and least frequent, the head and neck. Frequently radiation occurred to more than one area in the same case In two cases radiation occurred to the lower extremities, and in one, to the kidney regions In many cases the sensation in the area of radiation was different from that in the area of its origin In some cases the main pain originated in various areas outside of the chest and radiated to the anterior chest Pain occurred relatively more frequently in the entire anterior chest or in the retrosternal region and had a tendency to radiate relatively more often to the head and back in anterior left ventricular wall infarction than in posterior wall infarction In the latter, pain was relatively more frequent in the precordial region and radiated relatively more often to the neck, upper extremities, or epigastrium, and it was relatively more frequently absent than in anterior wall infarction Cerebral, gastrointestinal, and respiratory disturbances were commoner in posterior wall infarction

Radiation to both arms is relatively common, occurring in about one fourth as many cases as of radiation to the left arm alone. When only one arm is involved, the left is twenty-five times more likely to be affected.[109] It should be remembered that the chambers of the right heart and the sinoatrial node are right-sided structures In general, the severer the pain in the left arm, the more likely is there to be referred pain in the right arm too The likelihood of referred pain to both arms increases with advancing age; among 58 patients over the age of 50, there was pain in both arms in 30.[110]

RELIEF The pain of major infarction is not relieved by rest or nitroglycerin, stronger drugs being required, usually in large and frequently repeated doses Even intravenous administration of morphine may not afford relief. The pain abates somewhat after the first day, and after the second day opiates are seldom necessary. Rarely does pain persist after the fifth day.

OTHER CHARACTERISTICS Respiration rarely influences the pain of infarction; 10 per cent of one series of cases noted more severe pain on deep inspiration.[109] No pericardial or pleural friction rubs were present in any of the cases, so that the explanation for the pain is not clear. In pericarditis associated with myocardial infarction, the pericarditis seldom induces pain.

Often, the patient attempts to keep on working despite the pain of the infarction, in contrast to the patient with angina pectoris, whose pain makes any effort impossible, or to the malingerer.[63]

The pain of infarction, it has been reported, is more likely to subside if the heart fails, and is less severe in the presence of congestive heart failure I have not been able to confirm this observation.

PROGNOSTIC FEATURES The severity of the pain seems to bear little relation to the ultimate outcome; patients with mild pain are just as likely to die as those with unbearable pain A more favorable prognosis has been reported for patients with radiation of pain than for those with pain in one site.[8, 11] The poor prognosis reported for patients with purely abdominal pain[8] may be due to the fact that in such atypical cases the diagnosis is missed at first, and the treatment is delayed.

"PAINLESS" INFARCTION

Pain is usually a conspicuous feature of coronary disease, but even advanced atheromatosis may be present without causing pain and may be overlooked because the cardinal symptom, pain, is absent. Advanced disease of coronary arteries, at times with severe infarction, is often found by the pathologist, although the clinical history contained no mention of pain. Acute painless myocardial infarction, however, occurs only rarely, and even rarer is the absence of symptoms or "pain equivalents" in the presence of myocardial infarction. The abundant literature on this aspect of the problem is confused and misleading. Failure to distinguish between painless infarction and symptomless or silent infarction is a common error. The figures on the incidence of painless infarction vary all the way from 1 to 75 per cent of cases.[5, 7, 8, 11, 18, 24, 30, 46, 63, 71, 73, 77, 79, 81, 86, 101, 109] In one study it was found that 98 per cent of patients under the age of 30 whose histories were reliable suffered pain, and 84 per cent of an older age group, "simple narrowing" of the arteries, rather than thrombosis, was present in a higher percentage of those without pain.[110] No conclusions can so far be drawn about which attacks—the first or subsequent ones—are more often painless. In a series of 28 cases studied postmortem, 4 had single fresh infarcts, 11 had both fresh and old infarcts, and 13 had old infarcts only.[46] In another report, 7.3 per cent of 136 patients had painless infarctions, of these, 5 had dyspnea, 4 had general weakness, 3 had palpitations, 2 complained of abdominal discomfort, 2 were in syncope, 1 complained of nausea, and 1 of vertigo.[79] A careful analysis of 1200 cases of myocardial infarction, not all of which were of a major type, revealed that "In 4.4 per cent there was no pain in any form; in 8.3 per cent the pain was felt in other areas than in the anterior chest region, and in 2.9 per cent the pain was very mild and insignificant, making a total of 15.6 per cent cases in which pain was of no help in the [illegible] not of [illegible] d was [illegible] diagnosis."[1,63]

The reasons for such a wide variation in published figures are not difficult to understand. For the statistics to be of value, many factors must be taken into consideration. The person who has gathered the figures—the pathologist or the clinician—is important, figures based on autopsy material are obviously higher, since the patient in whom diagnosis might have been missed during life can no longer be queried, on the other hand, figures based on clinical surveys cannot be considered completely accurate unless they have been checked by postmortem examination, the history competently taken, and cases of infarction developing during coma, semicoma, narcotization, congestive failure, and postoperatively excluded. Cases of sudden death must also be excluded.

History-taking in coronary occlusion is beset with many pitfalls. (*1*) The patient may be in no condition to answer questions. (*2*) Pain may not be a prominent or presenting symptom and may be overlooked in the presence of such dramatic findings as sudden congestive failure or pulmonary edema. (*3*) The location and/or the radiation of pain may be atypical, or the patient may so word his complaint that he gives the impression of not being in pain. (*4*) Complaints of painful or distressing symptoms, such as discomfort, constriction, substernal pressure, dull chest ache, distress, may be difficult to classify as pain.

In one well-studied series, it was found that in 91 per cent of the cases of recent infarction proved by autopsy, in which an accurate history had been taken, the classic pain of a coronary attack had been present.[42] This figure would have been even higher, had the correct diagnosis been made or suspected clinically and the patient closely questioned. Only 4 per cent of the cases were painless by the rigid criteria of the investigator, while another 4 per cent suffered from sensations described as constriction in the chest, burning, pressure, choking, indigestion, or chest discomfort.

Even those cases which can be accurately classified as painless, however, are not symptomless. Thus, in one series of 375 cases, in which 17 (4.5 per cent) were classified as painless, dramatic symptoms were completely absent only in 4, in the remaining 13 cases in this group there were various symptoms referable to the nervous system.

The role of pain in the symptomatology of myocardial infarction may be classified as fol-

lows: (*1*) conspicuous typical or atypical pain; (*2*) mild typical or atypical pain; (*3*) absence of "pain" but presence of pain equivalents or other sudden symptoms, suggesting the need of a cardiac survey; (*4*) symptomless infarction All four of these categories may be found in a sufficiently large series; in acute infarction, most cases will be in the first group.

Of the several explanations offered for the so-called painless infarction the one that may be applicable in the majority of cases is that the patient has a high pain threshold This may be determined roughly by Libman's[48] method: pressing on the styloid process of the temporal bone and observing the patient's reaction. In my experience, most patients in whom the pain is minor or atypical are insensitive to pain, as demonstrated by this method; enough exceptions are found, however, to make any definite conclusions impossible Other explanations that have been suggested[79] are. (*1*) "slow" infarction, with possible anesthesia due to slow destruction of local blood vessels and nerves, (*2*) presence of pain equivalents; (*3*) sympathetic C fibers with an abnormal response to the stimulus of anoxia; (*4*) atypical coronary innervation; (*5*) areas of heart affected less sensitive to pain than other areas might be.

In the psychoses, painless infarction is reported to be common (67 5 per cent of cases), possibly because psychotic patients have lost the *meaning* of pain[30] Evans and Sutton[16a] suggest that cases associated with auricular arrhythmia or hypertension are more likely to be painless They believe that the slowness of infarction rather than the size of the infarct is likely to be the determining factor for the presence of pain

OTHER SIGNS AND SYMPTOMS

GASTROINTESTINAL MANIFESTATIONS Gastrointestinal symptoms are common in acute infarction and sometimes overshadow pain; the diagnosis of "acute indigestion" is still being made. In one series, nausea and/or vomiting occurred in 36 per cent of the cases; "indigestion" and diarrhea were present in a smaller number.[109] Nausea was present in 21 of 97 cases, in another series and in others there was belching.[23] In a third series, nausea and/or vomiting was found in 25 per cent of the cases; the prognosis was thought to be worse in these cases [11] In a series of 1200 cases of infarction, nausea, vomiting, gaseous eructation, "heartburn," "indigestion," and, rarely, salivation or dryness of the mouth were noted in 15 8 per cent of the cases.[89]

DYSPNEA This is the most frequent complaint, after pain At one time or another in the course of infarction, dyspnea occurs in a high percentage of patients (86 per cent, according to one investigator[11]) It may be the first complaint in some cases, and, rarely, it replaces pain

HICCUPS This may be a very troublesome symptom, requiring heroic therapeutic measures [83, 97, 103]

NEUROLOGIC MANIFESTATIONS These are discussed on page 129

WEAKNESS AND FAINTNESS These symptoms are usually part of the picture of shock, but may occur in its absence. According to one report, about half the cases of infarction feel some weakness or faintness, while in another large series weakness was a complaint in 18 2 per cent of the patients [89]

"SENSE OF IMPENDING DISSOLUTION" As in severe angina pectoris, many patients with myocardial infarction are sure that they are about to die Segmental visceromotor reflexes which increase the tonus of thoracic muscles and produce a sense of constriction, and reflexes to the stomach and gut which reduce tonus and cause a sinking feeling in the epigastrium may be some of the factors responsible for this sense of impending death.[106] The pain, nausea, weakness, and reflex constriction of the cutaneous vessels with a resultant subjective feeling of coldness all serve to heighten the sensation that death is near.

CYANOSIS This is frequently seen in patients with acute infarction—in 91 of one series of 135 cases,[59] and in 50 per cent of another series [11]

SWEATING Many, probably most, infarctions are accompanied by sweating, the

more severe the infarction, the more pronounced the sweating In one large series, 62 9 per cent of the patients with all types of infarction experienced some sweating.[84]

CARDIAC SIGNS OF MAJOR MYOCARDIAL INFARCTION

PERICARDITIS

The pericardial surface of the heart is frequently involved in major infarction, more often in older patients than in those under the age of 40 [119] The pericarditis may not be evident by any physical signs. In one series of 34 cases of recent infarction, 21 had pericarditis,[20] in another series of 60 cases that came to autopsy, pericarditis was found in 48 —localized in 36 and diffuse in 12.[98] Mural thrombi are usually present in pericarditis accompanying infarction.[102] Pericardial effusion is rare.[55, 85]

No matter which surface of the heart is involved, a pericardial friction rub may be heard however, the rub probably occurs more commonly with anterior infarctions—in one report, 14 out of 17 infarctions with friction rub were anterior [89] The reported incidence ranges from 1 in 108 cases[23] to 10 per cent or higher [11] In a series of 600 successive cases, I found a distinct friction rub in 57. The rub may be heard within a few hours, but most often in the second 24 hours It is not as loud, widespread, or prolonged as the rub of acute pericarditis.

In my experience, pain cannot be attributed directly to the pericarditis of coronary disease. Pericarditis is probably negligible clinically except as a minor confirmatory sign in the diagnosis, and as a contributory factor in the hemopericardium which sometimes occurs in the course of anticoagulant therapy.[60] In 2 cases, hemopericardium followed an organizing fibrinous pericarditis [2]

HEART SOUNDS AND MURMURS

Phonocardiographic study[57] of the heart sounds after myocardial infarction has confirmed the long-held impression of clinicians that the first heart sound is frequently impaired. These changes were due to loss of amplitude in the central group of vibrations, where the highest amplitude is usually found, no changes from normal were noted in the number of vibrations, the duration, and the average frequency of the first sound. The first sound was impaired soon after the infarction occurred in 79 per cent, and especially in those with signs of heart failure. After coronary occlusion, the impairment of the first sound often persisted long after the patient had regained a normal status in other respects The presence of a "poor, distant, or muffled" first sound for which there is no adequate explanation must therefore be considered a diagnostic sign of some importance.

In all cases with an impaired first heart sound, the second sound was increased in relation to the first, and in 11 of 78 cases the amplitude of the second sound showed an absolute increase There is no clear explanation for this

An auricular sound was found in 83 per cent of the cases; the sound was abnormally high and formed a presystolic gallop rhythm in 33 per cent A third sound was found in 12 per cent of a control group and in 47 per cent of the patients with coronary occlusion; in 9 per cent of the latter group, the amplitude was increased, forming a protodiastolic gallop rhythm In all, 47 per cent of the cases of coronary occlusion manifested gallop rhythm

The heart sounds after myocardial infarction were also studied by means of the vibrocardiograph, which records the inaudible vibrations as well as the audible frequencies of the heart sounds.[43] The first sound was found to be impaired, and there were changes in the inaudible complexes, these changes were fairly constant, but similar changes have at times been noted in other conditions

In itself, infarction generally does not produce a murmur except in the presence of heart failure or cardiac perforation, as of the septum, papillary muscle, or ventricular wall However, myocardial infarction occurs frequently in persons with heart murmurs, especially the often loud systolic murmurs associated with sclerotic changes in the aorta endocardium, or annulus fibrosus

BLOOD PRESSURE

The behavior of the blood pressure in myocardial infarction depends on whether the superficial or deep muscles are affected.[78] The pressure may not drop at all if the infarction

is minor. Early in the acute phase of a major infarction the blood pressure may rise somewhat. This increase, which does not persist once the infarction is complete, may be due to pain[14] or to a temporary peripheral vasoconstriction compensating for a coincident drop in cardiac output.[27, 104, 106] Insistence on a fall in blood pressure for establishing the diagnosis of an infarction is most unwise.

In most patients, however, there is a perceptible decrease in the blood pressure, which almost invariably follows the onset of pain, sometimes at once and sometimes one to several days later, *i e*, when the infarction is complete. The absolute decrease is greater in patients with antecedent hypertension, but more patients with normal pressure show a rapid drop. It is noteworthy that in the former group a blood pressure which seems normal may in fact represent a significant drop from an earlier high level According to one report, in about 20 per cent of patients with an initial systolic pressure of over 200 it did not fall below 150.[61]

A transient fall in pressure to 100 or less, seldom lasting for more than a few minutes to an hour, sometimes occurs on the first day of an attack, but soon returns to levels which are not alarming, especially if the pain is relieved or oxygen is given The infarction then runs its course without shock.

HEMODYNAMICS IN ACUTE INFARCTION

Studies on the hemodynamic features of acute infarction are not numerous Table 12 gives the data found within 1 week of acute myocardial infarction in 397 patients[4] The results of another study of 39 patients by the dye dilution technic are extremely interesting.[25] They are given in some detail below.

1. The stroke volume and cardiac output were within normal basal limits in most of the patients, but in many of the more seriously ill both were considerably diminished It is probable that the stroke volume decreases at the onset of every infarct, and that the hearts with the graver injuries do not compensate for this fall.

2. The peripheral resistance was increased in the early stages of infarction in most of the patients, but fell later. It seems unlikely, therefore, that the shock in infarction is caused by peripheral collapse.

3 The venous pressure did not deviate greatly from normal for the group as a whole, although there was some increase in the more seriously ill patients. However, the pressure decreased significantly during a 4 week observation period, even though the initial levels did not seem to be high.

4 The circulation time ranged from 12 to 60 seconds in 27 patients studied with dehydrocholic acid (Decholin), the mean value being 22.7 seconds. The average decrease in patients after several weeks was 3.1 seconds.

5. The system volume in the seriously ill patients did not differ much from that of other patients, another indication that the decreased cardiac output in infarction is the result of myocardial failure rather than of decreased venous return to the heart. This finding agrees with that of other investigators.[25]

6 The blood volume was slightly lowered, a finding of other investigators too. Transudation of fluid into the lungs, diaphoresis, vomiting, reduced fluid intake, and increased

TABLE 12. SIGNS OF HYPODYNAMIC CIRCULATION IN 397 PATIENTS WITH ACUTE INFARCTION[4]

Sign	*Per cent of cases*	*Sign*	*Per cent of cases*
Cardiomegaly	60	Ankle edema	22
Fall in blood pressure	51	Gallop rhythm	22
Pulmonary congestion (rales)	49	Pulse pressure<25 mm Hg	15
Congestive heart failure	37	Frank circulatory collapse, "shock"	15
Cyanosis	33	Venous distention	14
Dyspnea	32	Generalized edema	8
Hepatomegaly	31	Ascites	7
Weak or thready pulse	30		

venous pressure with the increase in filtration of fluid from the capillaries are some of the explanations suggested for the reduced blood volume.

A study on 5 patients who were not in shock showed a significant decrease in cardiac output.[33] This was also found in a ballistocardiographic study.[94] A recent survey has also found the cardiac output to be low, as a rule, the cardiac index (L./min./sq. M. body surface area) averaging 1.8±0 8.[27] Ballistocardiographic and pressure-pulse measurements confirmed the lowered cardiac output. Occasionally, a normal or elevated cardiac output was found in the early stages of infarction

In experimental coronary occlusion, the cardiac output decreased and the circulation time increased; the fall in blood pressure was not significant, although the decrease was greater in animals with previously denervated hearts [33]

Except when the cardiac output is extremely low, the blood pressure is sustained by increased peripheral resistance The venous pressure is usually increased, and the circulation time prolonged In general, the increase in circulation time corresponds fairly well with the severity of the infarction

Plasma volume has been reported by some workers[7] to be low in infarction, but not to be particularly low by others [27]

HEART FAILURE Most patients with myocardial infarction suffer some degree of heart failure. A workable classification of such failure would be: (*1*) predominant failure of left ventricle, as manifested by dyspnea, orthopnea, pulmonary edema, and other signs of increased pressure in the pulmonary circuit; (*2*) failure of right ventricle only, as manifested by distended veins, enlarged liver, ascites, edema, increased venous pressure, etc.; and (*3*) a combination of both types of failure.

Congestive failure was the most frequent complication of infarction in one series, one third of the patients manifesting heart failure either on admission to hospital or during the hospital stay.[11] In another series, heart failure was present in about two thirds of the 140 patients with coronary thrombosis; there was evidence of left ventricular failure in 18 per cent, of combined right and left ventricular failure in 48 per cent, and no evidence of isolated right ventricular failure in any.[59] These findings support White and McGinn's[105] suggestion that failure of the left ventricle is often responsible for right ventricular failure so that signs of combined decompensation appear. In other words, while infarction usually involves the left ventricle only, the resulting heart failure is of the combined type

Efforts have been made to show that right coronary artery occlusion results in dominant right ventricular failure, and similarly on the left. Thus, several cases of rapid hepatomegaly soon after occlusion of the right coronary artery have been reported.[49] Involvement of a large portion of the interventricular septum, it has been suggested, results in right ventricular failure, distention of neck veins, high venous pressure, and engorged liver [22, 49] Electrocardiographic and postmortem studies led to the conclusion that the type of heart failure gave no clue to the site of the infarct [59] In cases of early and severe right-sided failure, I have felt that the interventricular septum is often badly involved, but that it would not be safe to assume that the lesion is therefore in the right coronary artery only.

Heart failure occurs much more frequently in patients with a previous occlusion or coronary disease, and in patients with cardiac enlargement Heart failure is also much more likely when the infarcted area is large and more than one artery is involved. Patients with severe heart failure have less chance of surviving the acute period of infarction than patients with little failure

The test of vital capacity, which Master and co-workers[59] thought the most reliable test of heart failure, is not suitable for routine use in infarction and should be avoided The venous pressure was reported to be elevated in 24 of 33 cases; clinical evidence of congestive failure was found in 14 of the 24 patients.[67]

PULMONARY EDEMA This is a fairly common symptom in cardiac infarction. Among 140 cases of coronary thrombosis, 20 (14 per cent) had massive pulmonary edema; 70 per cent of the latter group had had a coronary occlusion earlier, 85 per cent had antecedent hypertension, and in 95 per cent the heart was enlarged.[59] Obviously, therefore, pulmonary edema usually occurs in patients

with long-standing cardiac hypertrophy in addition to the infarction. The prognosis is poor, with a mortality rate of 50 per cent. Roentgenographic evidence of pulmonary congestion is sometimes found, in the absence of physical signs, such as basal rales

FEVER Most, if not all, patients with major infarction have fever: in one reported series, 100 per cent of cases,[87] and in a series of my own 92 per cent of 400 cases Usually, the temperature rises within 24 hours of the onset, is at its height at 48 to 72 hours, and then subsides, so that unlike the sedimentation rate the temperature is once more normal within a week. Fever of longer duration almost always indicates a complication, often thrombosis or embolism. The temperature generally is 102° F. or less, although occasionally it may rise to 103° F. or higher It has been reported that the prognosis is somewhat worse when the temperature is high;[59] however, the correlation is a rough one, and many patients have made good recoveries despite high fever.

The fever is commonly interpreted as the result of absorption of the necrotic material in the heart This may be true, but there is experimental evidence that in some animals infarction after ligation of a large coronary artery is not accompanied by fever.[17] Even when the rise in temperature is accompanied by rales, it is not usually a sign of pneumonitis Although many administer antibiotics at the first appearance of fever, I am not convinced that such therapy is necessary

LEUKOCYTOSIS An increase in leukocytes occurs in more than 90 per cent of patients[57] within 24 hours, and is at its height by 72 hours In the absence of complications, the leukocyte count has returned to normal by the eighth day. Most often, the count is below 15,000, in rare cases, it may go up to 85,000 or higher.[12] In general, the higher the count, the greater the infarcted area and the worse the prognosis. In one series, the mortality rate for patients with counts between 10,000 and 15,000 was 13 per cent; for those with counts over 20,000, 38 per cent.[95]

The differential count is also changed, the percentage of polymorphonuclear leukocytes rising and reaching the highest level at about the same time as the height of the leukocytosis. Usually, the differential count and the total leukocyte count revert to normal at about the same time

Eosinopenia is usually present at the onset of an infarction.[21] An increase in eosinophils has been interpreted as a favorable sign.[29] A normal eosinophil count (over 50 per cubic millimeter) makes the diagnosis of early acute infarction unlikely Only 15 per cent have counts above this figure on the third day and only 3 per cent on the first day of infarction.[52a]

LABORATORY FEATURES OF ACUTE INFARCTION

An increased sedimentation rate, fever, and leukocytosis, all resulting from a consitutional reaction to tissue destruction, are valuable confirmatory signs of a major myocardial infarction. They correlate almost directly with the extent of the lesion, and fairly well with one another, but they differ in the rapidity with which they appear in the course of the illness and their return to normal levels In some cases, one or two of this triad may be normal, and the figures for each must therefore be interpreted in the light of the total clinical picture. Thus, if the ischemia is the result of a temporary coronary insufficiency, as in angina pectoris, the values will be normal; if the infarct is small or the involvement is subendocardial, the values will also be normal or almost so; values will also be normal if the tests are performed before or immediately after completion of the infarct and before significant absorption has occurred Reports in the literature should be interpreted with this in mind.

SEDIMENTATION RATE

The value of obtaining the sedimentation rate in coronary disease was suggested some time ago[70] Since then, our ideas about the sedimentation rate and its clinical significance have become considerably modified.[74] In most cases of major infarction (97 per cent in my series of cases), the sedimentation rate is rapid early in the course of the infarction, but if there is occlusion of small vessels only or if the infarction is subendothelial the rate may be hardly or not at all increased The increase in the sedimentation rate seldom appears earlier than 24 hours after completion of the

venous pressure with the increase in filtration of fluid from the capillaries are some of the explanations suggested for the reduced blood volume

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cedures. The first and third technics, respectively, measure a product of the enzymic transamination following a fixed period of incubation of serum with specified substrates under optimal and standardized conditions. The spectrophotometric assay relates the rate of oxidation of reduced diphosphopyridine nucleotide by serum to the rate of transamination through a coupled enzyme system.

The paper chromatographic technic is laborious, requires about 48 hours for completion, and necessitates considerable space and special equipment; it is not generally applicable to clinical use.[41] Colorimetrically, serum transaminase activity can be determined simply, and the technic requires equipment and reagents which are generally available in a clinical laboratory, this procedure uses larger samples of serum and is less accurate than the spectrophotometric method, but is satisfactory for clinical purposes.[98]

The spectrophotometric procedure is simple, rapid, and accurate, but requires the use of either malic dehydrogenase or lactic dehydrogenase.[33, 42] Although formerly requiring an expensive spectrophotometer, the technic has been modified and adapted to use with a simple colorimetric spectrophotometer.[70]

The transaminase test seems to be more specific, therefore more useful, than the sedimentation rate and most of the tests mentioned below. In the absence of liver disease and cancer, a sharp rise in the SGO-T level usually indicates myocardial necrosis. Other enzymes in cardiac tissue, such as lactic dehydrogenase,[107a] released after injury to myocardial cells, give promise of being as useful as transaminase when employed in the same way to help in the diagnosis of myocardial infarction.

PLASMA FIBRINOGEN

There is a prompt rise in the fibrinogen level at the onset of an acute infarction.[62] The plasma fibrinogen may be accurately determined by a photoelectric method, even in patients receiving anticoagulant therapy.[53] The correlation between plasma fibrinogen levels and the clinical course of the infarction seemed to be closer than the correlation between clinical course and sedimentation rate, the level was found to return to normal within 3 weeks.[31] Values of 800 mg. per 100 cc. and over were found in a group of gravely ill patients, the mortality rate in this group was 42 per cent. In patients with a moderate rise in plasma fibrinogen, the mortality rate was 9.7 per cent.[55]

URINARY UROBILINOGEN[16]

By serial semiquantitative determinations the urinary urobilinogen was found to be increased within 8 days of onset of an infarction. The investigators felt that this was "due to impaired liver function induced by a stress reaction" to the myocardial infarct, no evidence of a correlation with other symptoms or with the prognosis could be found.

URINARY COPROPORPHYRINS[15]

The daily excretion of coproporphyrins by healthy subjects ranges between 21 and 142 µg. In myocardial infarction, the excretion during the first 2 or 3 days ranges between 207 and 310 µg, and a similar increase was found in pulmonary embolism. The cause of this metabolic change is not clear, but probably is not related to shock, or, so far as could be determined, to deranged liver function.

SERUM MUCOPROTEINS

The serum mucoprotein level rises after myocardial infarction,[85] but its diagnostic significance is no greater than that of the sedimentation rate.[50]

SIGNS OF INCREASED CATABOLISM

The following evidence of increased catabolism was found in myocardial infarction, even in the absence of shock.[1a] (*1*) Creatinuria, confirming the finding of other workers.[36] (*2*) Negative nitrogen balance. (*3*) Increase in blood nonprotein nitrogen. (*4*) Slight rise in blood levels of lactic, pyruvic, and amino acids. (*5*) Occasionally, jaundice, probably due to depressed liver function.

ELECTROPHORETIC PATTERN OF BLOOD PROTEINS

The α_2-globulins increase during the first months after an acute infarction, the prognosis may be less favorable in patients in whom the values have not returned to normal after 2 months.[65] A slight decrease in albumin and an increase in α_1- and α_2-globulins and fibrinogen was found in 2 patients.[82] These changes, however, are not specific, since they occur in any condition associated with tissue necrosis.

The serum lipoproteins may be affected in coronary disease (*see* Chapter 4), but there is as yet no definite evidence of specific changes during acute infarction. Small amounts of cold-precipitable globulins (cryoglobulins) have been found in the serum of 40 per cent of patients with coronary disease, but the significance of this finding has not yet been determined.[10]

C-REACTIVE PROTEIN

This α-globulin, which appears in the serum when there is inflammation anywhere in the body, forms a precipitate with the somatic-C polysaccarides of the *Pneumococcus*. The test is positive in a high percentage of patients with myocardial infarction, but negative in coronary insufficiency without evidence of muscle necrosis[44] It may become a useful confirmatory test of infarction, much like the sedimentation rate, but, like it, nonspecific

PLASMA CHOLINE ESTERASE

The choline esterase activity in plasma has been reported to be decreased during acute infarction, and to revert to normal during recovery[63]

BLOOD POTASSIUM

In 10 cases of myocardial infarction, the potassium level in the blood was found to be increased, the increase was not associated with a decrease in the serum sodium level in every case[107]

URINARY EPINEPHRINE

Increased excretion of epinephrine was found in patients with infarction[45] The ratio of catechol derivatives in hydrolyzed and unhydrolyzed urine was also increased in infarction.

BLOOD COAGULABILITY

An increased tendency to clotting has been found in a high percentage of cases early in the course of infarction by the use of special tests, such as the heparin retarded clotting method of Waugh and Ruddick.[37, 67, 73, 82] Three phases have been described (*1*) a very constant period of hypercoagulability for the first 24 to 48 hours, (2) hypocoagulability from the third to the fifteenth day in 81 4 per cent of cases; and (3) a period of late hypercoagulability starting from the fifteenth day and lasting for several weeks or months. These findings may be important in sifting out patients for anticoagulant therapy. Hypocoagulability in most patients has been reported by some investigators,[13, 72] but the bulk of present evidence seems to indicate that the reverse is true.

ELECTROCARDIOGRAPHIC, BALLISTOCARDIOGRAPHIC, AND ROENTGENOGRAPHIC FEATURES

These are discussed in detail in Chapters 10 and 12.

CAUSE OF DEATH IN INFARCTION

Immediate death, or abrupt, sudden, or unexpected death seconds to hours after onset of the infarction is almost without fail the result of ventricular fibrillation or of ventricular standstill, with the deaths probably about equally divided between these two causes The terminal mechanism has been observed in a few cases in man: 1 case of ventricular fibrillation and 1 case of ventricular standstill after an attack of ventricular tachycardia have been reported.[29] Ventricular standstill has been demonstrated,[31] and ventricular fibrillation has been shown on electrocardiograms.[91]

Reflex coronary constriction has been suggested as a cause of sudden death in infarction, on the assumption that the efferent pathway is in the vagus,[47] this hypothesis could not be confirmed.[69]

Death within the first few days may still result from these causes, especially if there is interference with the remaining coronary circulation, as for example, by a sudden drop in blood pressure or by the abrupt occlusion of a small but vital anastamotic channel. In the rest, death is usually due to a complication In the first day or two, this is usually shock; thereafter, heart failure, cardiac rupture, or thromboembolism may cause death.

Table 13 shows the causes of death in 133 fatal cases of acute myocardial infarction.[84] The classification "coronary failure" applies to cases in which cardiac pain occurred during convalescence from an acute infarction and was followed by death; there had been no additional acute infarction, and presumably the pain was due to myocardial ischemia not

TABLE 13 CAUSE OF DEATH IN 133 CASES OF MYOCARDIAL INFARCTION[34]

Cause	Number of cases	Percent of total
Myocardial failure	57	43
Predominantly right	29	22
Predominantly left	17	13
Combined right and left	11	8
Coronary failure	31	23
Cardiac rupture	20	15
Shock	12	9
Thromboembolic complications	8	6
Systemic	4	3
Pulmonary	4	3
Miscellaneous	5	4

severe enough to cause new infarction but sufficient to kill the patient, possibly by causing a change in the cardiac rhythm.

Hellerstein[34] has introduced the terms "mechanism death" and "muscle death" to explain the common ways in which life stops in coronary heart disease Mechanism death occurs when the heart is able to continue working but beat coordination is impaired Sudden exertion or excitement may produce this condition without recent lesions being present in the heart According to some,[110] neither recent nor old myocardial infarcts are found in about a third of the cases of coronary death The importance of the "trigger area," an ischemic area of myocardium that is potentially able to send out impulses which derange the normal mechanism so that the muscle becomes incoordinated and convulsive is emphasized by Beck and Leighninger The trigger may be located in or at the border of a "dry area," a localized ischemic or relatively ischemic part of the heart It has been suggested, too, that intense spasm of the vasa vasorum of the smaller coronary vessels may be the terminal factor in some instances[25a]

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CHAPTER 9

Complications and Sequelae of Acute Infarction

ACUTE MYOCARDIAL infarction has many aspects Some of them, covered in the preceding chapter, may be considered an integral part of the initial process, while others are *complications which appear in a minority* of cases It is often difficult to tell whether a condition is a complication or a part of the original process, and an arbitrary distinction must be made for the sake of convenience

DISTURBANCES OF RATE AND RHYTHM

Acute myocardial infarction is commonly followed by a disturbed heart rate, while rhythm disorders are not as frequent (Table 14) The changes, varying from the common sinus tachycardia to such unusual conditions as complete heart block, are more likely to occur with posterior than anterior infarctions Arrhythmias were noted in over 33 per cent of the patients with severe posterior wall involvement in one series,[96] and in another large series some sort of arrhythmia was found in 16 3 per cent [121] Were transient extrasystoles included, the percentage would undoubtedly be much higher.

The frequent occurrence of irregular cardiac rhythms in myocardial infarction is not surprising *Direct involvement of the conduction* system, usually the septum, in the infarction as a result of tissue necrosis or of temporary ischemia or edema causes various errors of conduction. However, even when these tissues are not directly involved, ectopic rhythms may arise at the border of an infarcted area,[22] what ever the segment of heart involved Just outside the affected area, at the boundary between necrotic and healthy tissue, there are usually irritable foci from which impulses arise to produce ventricular premature contractions or runs of ventricular tachycardia, or, when transmitted in disorderly fashion, ventricular fibrillation.[138] However, not every ectopic beat which may be seen in the electrocardiogram elicits a mechanical systole. For the heart with an infarction, which is at the border line between efficiency and inefficiency,[139] any irregularity is disadvantageous, for it intensifies back pressure effects, reduces cardiac output, and lowers arterial pressure

TABLE 14. INCIDENCE OF ARRHYTHMIAS OBSERVED WITHIN ONE MONTH OF ACUTE EPISODE OF MYOCARDIAL INFARCTION IN 397 PATIENTS[44]

Arrhythmia	*Percent of cases*	*Arrhythmia*	*Percent of cases*
Tachycardia (pulse rate>110)	33	Bigeminy	5
Ventricular extrasystoles	24	First degree heart block	4
Ventricular fibrillation	17	Auricular flutter	2
Auricular fibrillation	11	*Pulsus alternans*	2
Auricular extrasystoles	9	Right bundle branch block	2
Bradycardia (pulse rate<60)	9	Ventricular tachycardia	2
Left bundle branch block	6	All other	9

The possible mechanism producing the excitability which in turn progresses to ventricular tachycardia is not known definitely Two phases of hyperirritability—an immediate and a delayed response—have been found in the area bordering an infarct after experimental coronary ligation.[52] Possibly, the potassium released from the necrotic cells of ischemic heart muscle may cause ectopic activity, neither histamine nor direct or reflex activity of the sympathetic nervous system seem to be causative agents [53]

PATHOGENESIS

The pathogenesis of the cardiac arrhythmias is still problematic, for involvement of the auriculoventricular node, except in cases of heart block, is rare Since atropine shortens the lengthened P-R interval in paroxysmal flutter or fibrillation after onset of infarction,[65] it has been suggested that excessive vagal activity may initiate the paroxysmal heart action, analogous to such action in thyrotoxicosis or rheumatic fever, or in experimental studies in animals Cutting the vagus nerve in dogs abolished the cardiac arrhythmias due to anoxemia [50] Numerous experiments with animals have shown that abnormal irritability may arise from an infarcted area, either from the dying muscle itself or from the immediately adjacent muscle tissue This irritability may consist of abnormal impulses or of abnormal reflexes, but in any case the necrotic area probably interferes with the normal conduction of the excitation wave

There may be no pathologic evidence that the auriculoventricular node is involved, but the possibility that altered metabolism of the tissues at these junctions as a result of anoxemia may be responsible for disordered rhythms is not ruled out.

The role of drugs in arrhythmias may be important It is known that both digitalis and quinidine can initiate ectopic rhythms, and some believe that ventricular tachycardia is uncommon after coronary thrombosis except in patients given digitalis

Cardiac arrhythmias would be even more common were it not for the fact that the subendocardial layer is often spared in large infarcts, and it is in this layer that many of the finer branches of the conduction system lie [18]

Auricular infarction may be responsible for auricular disturbances Auricular fibrillation and auricular extrasystoles were fairly common in one series reported [25] The possibility of such involvement must be borne in mind; in cases with auricular irregularities, a search should be made postmortem, if possible, for auricular lesions, especially in the presence of mural thrombi in the auricle.

SINUS TACHYCARDIA

Although it may be preceded by a period of slow or normal heart rate, sinus tachycardia occurs in well over half of all cases of infarction, usually within the first 3 days In one series, tachycardia was found in 98 per cent [119] The prognosis is generally graver when the rate is extremely or persistently rapid A rate of over 100 has been reported in 76 per cent of the patients who died, but in only 25 per cent of those who recovered In another series, this high rate was present in 8 of 17 patients who died, but in only 9 of 71 patients who survived, about 50 per cent of patients in this series at no time had a rate over 100.[60] Extreme, persistent, or late (after 3 days) tachycardia should lead to a search for an ectopic rhythm.

SINUS BRADYCARDIA

This transient disorder of heart rhythm occurs with some frequency in infarction within 8 hours of the onset, and is usually abolished by morphine. Prolonged Q–T intervals and high T waves have been found on the electrocardiogram [101]

GALLOP RHYTHM

This rhythm is found in 5 to 28 per cent of patients with acute infarction. Its persistence is of grave prognostic import [60, 119, 143] In one series, gallop rhythm was found in 51 per cent of the cases that ended fatally, and in 8 per cent of those who survived [103] It has also been reported that the prospect of recovery is not as good when gallop rhythm occurs early, especially in patients without antecedent hypertension.[129] Gallop rhythm has been reported to be more common with tachycardia

HEART BLOCK

Every degree of heart block may occur in the course of infarction, but while first degree block is relatively common, second and third degree blocks are fairly rare. A review of 2583

cases from the literature in which the heart rhythm was reported showed that second or third degree block was present in 6.7 per cent: second degree block in 4.8 per cent, and complete block in 3 per cent [133]

A prolonged P–R interval (first degree block, occurs in about a sixth of all cases prognostic implications of the other forms of block, occurs in about a sixth of all cases of acute infarction It may occur at any time after onset of the acute episode, and usually within 3 weeks; it is more likely to persist than second or third degree block. No apparently characteristic localization of the infarct has been found to be associated with prolonged P–R interval In second and third degree block, however, the posterior ventricular wall and adjacent septum are usually involved Among 54 patients with posterior infarctions, there were 1 case of first degree, 2 of second degree, and 2 of complete heart block; whereas no cases of heart block was found in 73 patients with anterior infarctions [48] Among the 2583 cases cited above, the posterior wall was involved in 60 cases, the anterior only in 7 [133] Advanced sclerosis of both major coronary arteries is present in most cases of heart block, especially in complete block.

Nevertheless, it would be wrong to conclude that thrombosis of the right coronary artery is invariably followed by heart block; actually, only 5 per cent of patients suffer heart block, the low rate probably being explicable by the extensive anastomoses in this area. In the exceptional case without necrosis of the auriculoventricular node and bundle, the block probably results from the anoxemia due to diminished blood flow, for the node is highly sensitive to oxygen lack The shock and resultant decrease in blood flow in infarction would thus explain the early appearance of heart block after infarction.

The prognosis for patients with infarction and second or third degree heart block is not good. The mortality rate in complete heart block was 58 per cent; in second degree block, 43 per cent; and in patients over the age of 60, 74 per cent.[133]

EXTRASYSTOLES

[illegible] ystoles are com- [illegible] ent, about [illegible]

irregularity at some time during their illness. In a series reported by Smith and associates,[123] 71 (7.7 per cent of the total) had nodal extrasystoles—7 auricular and 63 ventricular. The death rate was higher among the patients with ventricular extrasystoles (36.5 per cent); 37 of the 63 patients were treated with quinidine (death rate, 35.1 per cent), and 26 were not (death rate, 38 4 per cent).

Premature contractions were found in 11 of another series of 88 cases, 7 of these had posterior wall infarctions, and 2 of the patients died [60] In a third series of 77 cases with premature beats, 46 were ventricular, 14 auricular, 2 nodal, and 15 both auricular and ventricular, the mortality and heart failure rates were the same as for the patients without premature beats, except in the group with both auricular and ventricular beats, in which the mortality rate was 35 to 40 per cent.[82] The appearance of frequent ventricular premature beats was not believed to be a forerunner of ventricular tachycardia, this occurred in only 1 case of the series.[82]

Investigators at the Mayo Clinic, however, found an association between premature contractions of any kind and a higher mortality rate [142] All the cases of ventricular extrasystoles were divided into three groups (*1*) those with occasional (1 in 21 or more beats), and (*2*) those with moderately frequent (1 in 11 to 1 in 20 beats) extrasystoles all survived, (*3*) those with very frequent ventricular extrasystoles (1 to 10 or less cardiac beats), had a very high mortality rate, 82 4 per cent of the 17 cases dying in the acute period The appearance of extra ventricular contractions is an ominous sign, in their opinion, and in many cases is followed by ventricular tachycardia and fibrillation. I, too, am inclined to believe that ventricular premature contractions are an unfavorable sign, particularly when they are multifocal.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

This is a rare complication, as the following figures from the literature show: among 43 cases of arrhythmias, there were 3 of paroxysmal auricular tachycardia and 2 of nodal tachycardia,[82] 3 cases of auricular tachycardia in a series of 24 cases of paroxysmal *heart action during acute infarc-*

tion;[139] 2 cases of paroxysmal auricular tachycardia, with partial auriculoventricular block;[5] no paroxysmal tachycardia in a series of 88 cases of infarction,[60] 3 cases of auricular tachycardia and 4 of nodal tachycardia in a series of 920 cases,[123] 5 cases of paroxysmal tachycardia, all fatal, in a series of 1247 cases.[2]

AURICULAR FLUTTER AND FIBRILLATION

These, too, are rare Both occur most often in the first week of illness In one series, most of the irregularities subsided spontaneously within 36 hours and there was no increase in cardiac pain.[82] In two reports, the arrhythmias were stated to be about equally divided between anterior and posterior infarctions,[60, 123] the incidence would therefore seem to be higher in the posterior infarction group. A high incidence of fibrillation has also been reported in left lateral infarctions [130, 140] The prognosis, especially if the flutter and fibrillation persist, is grave;[58, 82, 123] in one series, all 8 patients with persistent flutter died, whereas only 36.3 per cent of those with transient flutter did not recover,[2] in another, 7 of 10 patients died;[58] in a third series, the mortality was doubled.[82] Other investigators, however, felt that auricular fibrillation did not influence the mortality rate [71, 97] The incidence of auricular flutter and fibrillation may be gauged from the following figures 16 with fibrillation in a series of 372 cases,[71] 7 per cent of cases;[82] auricular flutter in 4 and fibrillation in 3 of 88 cases;[60] 44 cases of auricular fibrillation and 4 of auricular flutter among 920 patients,[123] 7.7 per cent with fibrillation and 1.5 per cent with flutter in a series of 1247 patients [2]

VENTRICULAR TACHYCARDIA

This is generally acknowledged to be a sinister complication of about 2 per cent of the cases of acute myocardial infarction [116] Spontaneous reversion to normal rhythm is rare. The tachycardia is essentially a complete heart block with a rapid ventricular rate, and usually occurs within the first 2 weeks of the infarction Of 13 cases in a series of 920 patients with infarction, 11 occurred in the first 5 days and the other 2 on the fifteenth and eighteenth days, respectively,[123] both of the patients had been given digitalis. The site of the lesion was known in 12 cases anterior infarctions in 9 (6 died), posterior in 3 (1 died); site not determined in 1 fatal case.

In no other complication of acute infarction is prompt diagnosis and treatment so essential. Any change in rhythm and rate calls for immediate electrocardiography. When an electrocardiogram is not available quickly, ventricular tachycardia should be suspected if the intensity of the first apical sound is changing, if the length of the ventricular cycle is slightly irregular, and if the rate is not affected by vagal stimulation.[1] When the first and second sounds are single or normally split in a case of rapid, regular heart beat, supraventricular tachycardia may be safely assumed and ventricular tachycardia excluded with confidence. In general, ventricular tachycardia may be diagnosed with confidence if there is: (*1*) wide splitting of both heart sounds, (*2*) varied intensity of the first sound, and (*3*) independent, irregular "Cannon A" waves in the jugular venous pulse.[114] The first of these is the result of ventricular asynchrony; the second and third are manifestations of auriculoventricular dissociation

Supraventricular tachycardia, with bundle-branch block, may present diagnostic difficulties In this condition, wide splitting of the heart sounds may occur, but there is no variation in the first sound If the widened main complexes obscure the P waves, esophageal leads will bring out these waves clearly; but since most of these patients are close to an acute infarction, the use of an esophageal lead can be advised only hesitantly. Fortunately, the procedure is seldom necessary.

Rare conditions which must be distinguished from simple ventricular tachycardia are ventricular tachycardia with auricular fibrillation and retrograde conduction In these, the sounds are also split, but the first sound is of constant intensity.[114]

VENTRICULAR FLUTTER AND FIBRILLATION

These disorders are common terminal events, and are seldom found until shortly before death. Nevertheless, survival has been reported, as in 1 case of acute occlusion with ventricular fibrillation [26]

OTHER ARRHYTHMIAS

Auriculoventricular nodal rhythm, coronary sinus rhythm, wandering pacemaker, and

auricular bigeminy are both rare and unimportant; in a series of 127 cases, each was found in 1 case.[48]

BUNDLE-BRANCH BLOCK AND INTRAVENTRICULAR BLOCK

Disturbances of the intraventricular system are common in coronary disease, especially of the chronic variety. Among 1058 cases of acute coronary occlusion gathered from the literature, 12 per cent had such disturbances, the QRS interval was prolonged to 0.12 sec. or more in 57 of 375 cases (15 per cent).[84] Most of these cases were associated with old hypertension, cardiac enlargement, and congestive heart failure—in 77, 84, and 92 per cent, respectively In 29 cases there was the common type of left bundle-branch block, in 9, typical right bundle-branch block, in 9, atypical right bundle-branch block, characterized by a broad S wave in lead I. Intraventricular block was found in 10 cases

The conduction defect is sometimes transient, but more often appears on the first day of infarction, and persists In the series cited, the block increased the mortality rate to 42 per cent. With the exception of auriculoventricular block,[115] other arrhythmias are not commonly found in association

The electrocardiographic pattern of myocardial infarction is discussed in Chapter 10. The sudden appearance of this type of block should be regarded an an indication of recent coronary occlusion, especially if there are any confirmatory signs or symptoms The clinician then need not wait for characteristic changes in the electrocardiogram to make the diagnosis, serial changes, of course, are still of the highest diagnostic value.

WOLFF-PARKINSON-WHITE SYNDROME

Formerly this syndrome was thought to be entirely benign, but it is now known to occur in organic heart disease.[104] Six cases have been reported in association with acute infarction and with chronic coronary disease; in 5 the posterior wall was involved, in the sixth, the anterior wall.[46] Another case has been reported in association with septal infarction.

The P–Q interval has been reported as shortened, without changes in the main complex, in a high percentage (47 per cent) of acute infarctions.[15]

SHOCK

Shock is a justly dreaded complication of acute infarction. Statistics on the incidence of shock are not too reliable, since the criteria used by investigators vary widely; in addition, the figures must also vary with the definition of infarction The incidence reported ranges between less than 5 per cent and 17 per cent of cases[7, 20, 33, 37, 143] Reports giving an incidence of over 40 per cent probably included milder cases in the series.[11, 83]

The diagnosis of shock should be reserved for the combination of hypotension (below 80 systolic) for at least 30 minutes, associated with (*1*) a cold, moist, mottled skin, and often with cyanosis; (*2*) profound weakness or stupor, (*3*) rapid, small pulse (over 110), unless heart block is present; (*4*) superficial respirations; (*5*) oliguria or anuria.

It is still uncertain whether the principal cause of shock in infarction lies in the heart or in the peripheral circulation Cardiogenic shock is due to failure of the "central pump." The damaged heart is unable to pump out enough blood, despite sufficient venous return. Peripheral shock is supposedly due to profound peripheral vasodilatation, the mechanism in such cases being about the same as in traumatic shock.

Study with improved technics makes it increasingly clear that the main cause of shock in infarction is central pump failure, and that in many cases peripheral failure is an additional, but not the main, factor The balance between these factors probably shifts during the course of illness in any one individual, and it may not be the same in all patients In any case, the genesis of the clinical situation should be determined, if possible, since rational treatment depends on such evaluation

The compensatory mechanisms brought into play in cardiac shock with reduced systolic discharge are the same, whatever the cause of the reduced ventricular output may be[138] Vasoconstriction in the viscera results in increased peripheral resistance, with a rise in blood pressure. Vasoconstriction in the cutaneous vessels diverts blood from its capacious skin reservoir to internal organs. In ordinary shock such diversion serves to increase the venous return to the heart; in infarction, it

merely adds to the volume of blood which the defective myocardium must move In addition, the pulmonary congestion leads to respiratory reflexes which produce much more severe dyspnea than is seen in other forms of shock, since venous flow is retarded, the cyanosis is more intense than in peripheral shock.

The presence of shock indicates that the infarcted area is so large that the deeper muscle layers are involved. A drop in systolic pressure at this point, impeding the development of a good anastomotic bed, causes further damage of the myocardium. A good pressure difference across anastomotic channels is essential for adequate function of anastomoses The mean pressure in a peripheral coronary branch is about one fifth that of the aorta, if the latter changes, the proportion remains about the same

Shock, with its diminished cardiac output and low blood pressure, has disastrous effects on other organs Reduced blood flow to brain, kidneys, and liver may produce profound changes which may cause death regardless of what is happening in the heart itself

PERIPHERAL GANGRENE

I have seen several patients with gangrene of the nose and symmetric gangrene of the fingers, toes, or ears in the terminal stages of myocardial infarction complicated by shock (Fig. 33). A recent review of the subject points out that in low-output heart failure, the blood flow to various parts of the body is not uniformly reduced [12] There is an "order of sacrifice," so that the myocardium and brain remain fairly well supplied with blood, while the supply to the liver, kidneys, skin, and limb muscles is poor Varying degrees of vasoconstriction probably account for these differences, Fishberg and co-workers[30] accurately described this condition as "angiospastic in origin and the unfortunate side-effect of a compensatory mechanism"

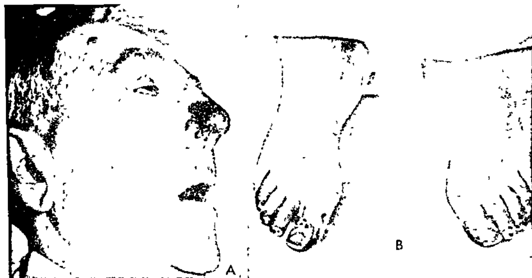


FIG 33 Peripheral gangrene in myocardial infarction A, Gangrene of the nose B, gangrene of the toes (From Bird et al)

CARDIAC RUPTURE

Rupture of the heart is a complication of fresh, major infarction, it does not occur in old infarctions, even in those with ventricular aneurysm It usually occurs with full thickness infarcts, often when a fresh infarct is superimposed on an old one [136] Rupture through an infarcted area is uncommon, occurring probably in less than 5 per cent of all cases of major infarction [134] It accounts for less than 10 per cent of deaths in acute infarction, judging by figures in the literature [29, 30, 40, 41, 45, 77, 91, 92, 119, 133, 137, 145]

Cardiac rupture may occur as early as the first day, but most often takes place in the first week, less often in the second week, and least often in the third week after onset of

the infarction It is almost never seen thereafter.[78, 119]

Rupture is as common in women as in men,[30, 77, 95] despite the sex incidence in uncomplicated infarction, and is more common in the older than in the younger age groups[95] With the exception of a fresh infarction at the site of an old one, rupture is more likely to occur in a first infarction,[122, 145] this may possibly be due to the inadequate collateral circulation when infarction first occurs Patients with pre-existing hypertension which did not regress after an acute infarction are more susceptible to cardiac rupture[80, 137] Rupture is least likely in the patient with a large heart and hypotension.[30]

Inadequate rest has been suggested as a predisposing cause of rupture,[21, 28, 92, 95, 137] and it may possibly be precipitated by effort. Thus, it is found more often among patients in mental hospitals and in medical examiners' autopsies[21] than in the general hospital population. In one series, there had been unusual effort in the last 24 hours of life in 61 per cent of cases with rupture, in comparison to 24 per cent of control autopsies[137] Nevertheless, absolute bed rest does not prevent rupture, on the other hand, no rupture has occurred among Levine's[69] patients treated by the armchair method Digitalis does not seem to increase the tendency to rupture,[95] whereas anticoagulant therapy may do so.

The three major types of cardiac rupture, in order of frequency, are rupture of the ventricular wall into the pericardial cavity, rupture of the interventricular septum, and rupture of the papillary muscle.

VENTRICULAR WALL RUPTURE

The lesion is usually of the "ragged dissection" type.[43] It starts through an area of myocardial necrosis with hemorrhagic extravasation. The infarction may not be of the full-thickness variety, and the rupture may dissect through healthy myocardium to reach the surface While minor tears probably occur in most cases of major infarction, continuation of the process depends on the plane in which the tear is initiated[117]

Ventricular wall rupture accounts for more than 80 per cent of all cases of cardiac rupture. The left ventricle is most commonly implicated, usually its anterior surface, somewhat less often its posterior surface. The right ventricle, the right auricle, and the left auricle are next, in that sequence. Spontaneous rupture of the auricle may occur without previous infarction.[3]

Survival after complete rupture is a matter of minutes to days. In 1 case, there was reason to believe that the patient lived for 3 weeks; the roentgenogram seemed to show a pericardial effusion.[67] Although in many cases death seems instantaneous, antemortem clotting has been found in the pericardial sac, sometimes with early organization.[28] Diagnosis during life is difficult. Rupture should be suspected when the patient's condition suddenly worsens, and signs of tamponade appear.

INTERVENTRICULAR SEPTAL RUPTURE

The tear may be located at any point of the septum, but in contrast to congenital lesions, is usually found posteriorly in the muscular portion of the septum near the apex Multiple septal ruptures may occur, or there may be tears through the free ventricular wall and the septum.[17] A dissecting aneurysm of the septum has been reported.[83]

Rupture of the interventricular septum is much rarer than ventricular wall rupture, occurring in 3 to 20 per cent of all cases of cardiac rupture In a series of 145 cases of myocardial infarction, 3 of the 14 ruptures were septal[45] More than 100 cases of septal rupture have been reported so far.[16, 45, 79] In some contrast to ventricular rupture, septal rupture shows little correlation with age, or with hypertension appearing after the infarction Of the reported cases, 34 per cent occurred in women Most septal ruptures occur within 10 days of the acute infarction, but may be delayed as long as a month, one report states that 98 per cent occurred within 16 days,[94] and in at least 1 case rupture occurred within 16 hours of the onset of symptoms of infarction[81] Death is not as sudden nor as quick as in ventricular rupture, but as a rule is not delayed beyond 8 weeks. Cases have been reported with survival up to 225 days[30] and even 6½ years.[112]

Septal ruptures are associated with severe coronary disease with occlusion or advanced narrowing of more than one artery. The usual combination is complete occlusion of the anterior descending artery, with marked stenosis of the posterior descending branch of the right artery.[108] Despite the frequency of septal in-

farction, perforations are rare, possibly because the septum receives an exceedingly rich anastomotic blood supply. Although the intraventricular pressure is normally twice as great on the left as on the right side, the difference is probably much slighter in myocardial infarction, in which the intracardiac pressure falls, especially on the left, so that the integrity of the septum tends to be preserved [38]

Septal rupture is characterized by the following features: To the clinical picture of myocardial infarction are added (*1*) Sudden worsening of the patient's state (pain may return after having subsided). (*2*) Development of gross right-sided failure, with dyspnea even at bed rest, cyanosis, and other signs of congestion. (*3*) Possible appearance of nausea, vomiting, and abdominal tenderness. (*4*) Common occurrence of peripheral circulatory collapse. (*5*) Possible occurrence of Bernheim's syndrome. (*6*) Development of a murmur not previously heard, usually a loud systolic murmur and best heard between the apex and the lower end of the sternum, it may be heard over the sternum or in the fourth or fifth intercostal space. (7) Presence of a thrill in most cases (*8*) Possible transmission of the murmur to the axilla (*9*) A diastolic component is very rare, and occurs only when the tear is very large [42] (*10*) Electrocardiographic changes in about 25 per cent of the cases, showing either right heart strain or a conduction defect, the latter rarely because the septum is usually torn in its more distal portion.

The diagnosis of septal rupture is often missed, but at least 26 cases have been diagnosed during life, and proved.[54] It has been suggested that the combination of signs of a posterior infarction and anteroseptal infarction helps in the diagnosis.[29] Septal rupture must be differentiated from pericarditis, sudden heart failure, and from rupture of a papillary muscle (Table 15)

PAPILLARY MUSCLE RUPTURE

This is the rarest type of cardiac rupture, since it was first noted in 1903 by Merat, some 40 cases have been reported All involved the left ventricle, and nearly all were in men Anterior infarctions involve an anterior papillary muscle, posterior infarctions, a posterior muscle Incomplete rupture of a papillary muscle,[57] and passage of the tree flap through the mitral valve,[21] have been reported From a study of the case histories, it would seem that 1 to 10 days may elapse after an infarction before the papillary muscle ruptures The patient may die suddenly, or may survive for a time, 1 patient lived for 20 months

This type of perforation should be suspected if within 10 days of an acute infarction the patient's condition suddenly grows worse and there is an abrupt onset of left ventricular

TABLE 15 DIFFERENTIAL DIAGNOSTIC FEATURES OF RUPTURED PAPILLARY MUSCLE AND RUPTURED SEPTUM

Feature	*Ruptured muscle*	*Ruptured septum*
Murmur	Heard in 50% of cases, usually systolic, but may be diastolic, to-and-fro, or bizarre, best heard close to apex, often clearly transmitted to axilla	Heard in over 90% of cases, almost always systolic, best heard parasternally in third to fifth interspaces, infrequently transmitted to axilla
Thrill	None	Heard in over 50% of cases
Pseudorub	Heard in 13%	Never heard
ECG	Original infarct pattern may be exaggerated	Right ventricular strain or conduction defects may be seen in about 25% of cases
Clinical picture	Left heart failure with pulmonary edema	Right heart failure of slower onset, venous and hepatic congestion if death delayed
Death	Usually soon after onset	Usually delayed

failure The pulmonary congestion is severe and intractable. A murmur, not previously present, is heard in more than half the cases—much less often than in septal rupture. The murmur is usually systolic, but occasionally diastolic, is loud as a rule, and may be to-and-fro It is sometimes described as bizarre or slapping It is best heard close to the apex, and is more apt to be transmitted to the axilla than is a septal murmur Thrills are unusual.

The following conditions must be differentiated from ruptured papillary muscle. (*1*) Rupture of the chordae tendinae, which occurs not in infarction but in subacute endocarditis. (*2*) Rupture of a mitral or an aortic valve, which does not occur in acute infarction. (*3*) Sudden left ventricular failure, in which the new murmur and its characteristics should prevent misdiagnosis. (*4*) External rupture of the heart, which in rare cases produces a loud, harsh murmur [13] (5) Coexisting coronary disease and rheumatic endocarditis, in which the murmur is not heard suddenly and lacks the bizarre quality noted in ruptured papillary muscle. (*6*) Rupture of the interventricular septum (*see* Table 15).

AURICULAR RUPTURE[50]

This type has been reported as a complication of auricular infarction in 17 cases. Auricular rupture occurs more often in men than in women Death comes quickly, but not quite as quickly as in ventricular rupture, 1 patient survived for 9 weeks The rupture is not usually preceded by unusual exertion. Thus far, auricular rupture has not been accurately diagnosed during life, but the electrocardiographic changes characteristic of auricular infarction should suggest it. The physical signs of tamponade, roentgenographic evidence of pericardial effusion, or aspiration of blood may indicate the presence of blood in the pericardial sac.

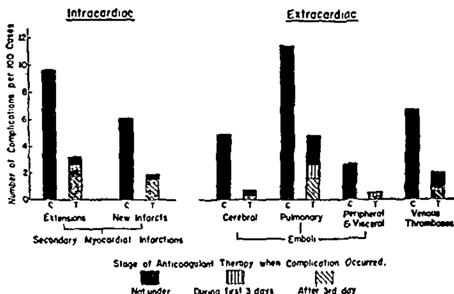


FIG 34 Thromboembolic complications of myocardial infarction (From Wright [142])

THROMBOSIS AND EMBOLISM

Thrombosis, and the resulting embolism, properly feared as complications of acute coronary disease, account for a large number of deaths and disabilities even in this era of anticoagulant therapy (Fig 34). Thromboses in the course of myocardial infarction may arise as: (*1*) further coronary thromboses at the same or new sites, (*2*) mural thrombi within the cardiac cavity, (*3*) venous thrombi, especially in the lower extremities, and (*4*) arterial thrombi outside the heart.

If mural thrombosis is included, clots at locations other than the initial lesion are found in well over half the cases of major myocardial infarction. The comprehensive re-

view by Wright[142] gives the latest statistical findings

NEW THROMBOSES WITHIN CORONARY ARTERIES

Acceptable statistics on this complication are not yet available, but the occurrence of extension of an original thrombus is unquestionable It is equally certain that new clots form in other arteries, and that this accounts for a high morbidity rate. This is scarcely surprising, in view of the increased clotting tendency in myocardial infarction and of the likelihood of a sharp drop in blood pressure with a resultant increase in thrombus formation. The thrombus need not be in a large artery to be disastrous; obstruction of a small anastomotic channel may be the final blow for an infarcted area receiving just enough blood from the vessel to stay alive or to prevent extension of the necrosis The impediment to the blood flow in a small vessel may be not a clot but a clumping of red cells in a still flowing stream, the phenomenon of "erythrocyte aggregation"[23] This reaction occurs after, not before, infarction, and may appreciably hamper the effectiveness of the collateral circulation

MURAL THROMBI AND RESULTING EMBOLISM

A clot forms on the inner surface of a major infarction in more or less half of the cases[8, 88 63 113, 134 136 144] The thrombus probably starts forming within hours of the completion of an infarct, and it may form and embolize before other signs of a heart attack become noticeable Thrombosis, which may start early in large infarctions, is usually well established by the ninth day and organization is often complete by the sixteenth day[75]

The determining factors in thrombus formation are the size of the infarct, and the presence of congestive failure and cardiac dilatation; both failure and dilation impede the emptying of the heart. Mural clots are found more often in association with large infarcted areas (40 sq cm or more)[63] They may occur as fresh or only partly organized thrombi in comparatively old infarcts, and may therefore be secondary to later cardiac dilatation

Mural thrombi occur most often in anterior wall infarctions with apical involvement,[63] but are also frequent with posterior wall infarction The thrombi are usually found within the left ventricle, either on the free ventricular wall or the interventricular septum.[106] Several examples of thrombi in the right ventricle and right auricle have been reported[125]

These clots on the wall of the heart may serve a useful function in strengthening a weak, necrotic area. Nevertheless, they are justly feared for their tendency to embolize to the brain and other parts of the body.

Cerebral embolism, resulting in hemiplegia[8] or other neurologic disturbances, is not a rare complication of myocardial infarction Its origin is a clot forming in the left side of the heart. Hemiplegia may even be the presenting feature of an acute coronary episode, the "cerebral debut" of infarction. Thus, in 13 cases of painless infarction, there were dyspnea, sudden nausea or vomiting, fainting or collapse, vertigo, or hemiparesis The dramatic features of a stroke may so obscure its cardiac origin that the latter is completely overlooked Painstaking clinical and electrocardiographic study of the hemiplegic patient in whom the diagnosis is in doubt would eliminate such errors

The cerebral blood flow may be reduced in the absence of arterial or venous thrombosis, and result in transient focal neurologic signs Emboli were found in only 9 of 15 cases of infarction with hemiplegia, and reduced blood flow in 6[7] Cerebral ischemia due to reduced flow is more likely to cause cerebral necrosis at sites where the blood supply is already impaired by arteriosclerosis.

Loss of consciousness (syncope) may occur as part of the picture of shock, or as an isolated phenomenon in infarction It may be the initial sign of infarction,[23] and occasionally syncope may occur in the absence of pain, acting as a "pain equivalent" In one series, 11 per cent of the patients were unconscious at one time or another,[143] and in a second series, 12 5 per cent of the patients[60] Syncope with convulsions may occur as part of the Stokes-Adams syndrome. Sudden, otherwise unexplained syncope calls for thorough cardiac study.

One report states that "nervous manifestations" were present in 18.5 per cent, 4 per cent of this group had convulsions; 6 per cent complained of dizziness; 5 patients had hemiplegia[143] In another series of 1200 cases, 21 6 per cent had some neurologic symptom dizziness, lightheadedness, restlessness, apprehen-

sion, faintness, syncope, or local tonic or clonic convulsive movements; and 7.2 per cent had chills, heat sensations, flushing, and shivering.[120]

Cerebral hemorrhage may occur in association with embolism, with reduced blood flow, or independently.

Emboli may reach the spinal cord, rather than the brain. In a patient of mine, a man of 50, signs of a transverse cord lesion were due to a small embolism from a mural thrombus in the course of an otherwise almost symptomless infarction.

Arterial emboli originating in the mural thrombus may settle anywhere within the greater circulation. Emboli to the great arteries of the extremities commonly cause death, whether surgery is prompt or not. The emboli may occur in any of the extremities, but usually in the lower Of 8 patients with infarction and emboli in the extremities who had not received anticoagulant therapy, 6 died; none of the patients had had adequate bed rest[69]

Among 589 patients treated with anticoagulants, 4 had cerebral emboli (1 of which was possibly a thrombus), 2 had renal emboli, and 1 an embolus in the arm; among 442 patients not given anticoagulants, 20 had cerebral emboli (or thrombi), 4 had emboli in the lower extremities, 4 had aortic emboli (including 1 saddle embolus at the bifurcation of the aorta), 1 had an embolus in the right axillary artery, 1 in the mesenteric artery (possibly a thrombus), and 1 in the renal artery.[142]

VENOUS THROMBOSIS

As in any disabling illness, venous thrombosis, especially in the lower extremities, often occurs in myocardial infarction. Of 589 patients given anticoagulants, 12 had venous thrombosis, of which 10 were in the legs, 1 in the arm, and 1 in the left jugular vein; of 442 patients not given anticoagulants, 28 had venous thrombosis.[142]

ARTERIAL THROMBOSIS

This probably occurs more often than was formerly believed. Some "emboli," for example, those in the brain or in the extremities, are actually thromboses *in situ*

PULMONARY EMBOLI

This complication is unexpectedly frequent in myocardial infarction. Of the 589 anticoagulant-treated patients, 28 had pulmonary emboli; of the 442 patients not so treated, 48 had pulmonary emboli. Some of these emboli have their origin in thrombi of the right side of the heart, but the majority come from areas of phlebothromboses in the lower extremities Pulmonary embolism does not necessarily result in pulmonary infarction. If the emboli are small, the collateral circulation through the bronchial arteries or other pulmonary arterial branches often suffices to prevent death of lung tissue, a large embolus, on the other hand, may cause the patient's death so quickly that changes in the lung tissue may not have taken place.

GLYCOSURIA

It is well known that infarction is a frequent complication of diabetes mellitus, but that glycosuria may occur only during the stage of active infarction and not represent true diabetes mellitus is less well known. In a study of coronary thrombosis, 25 per cent of the patients had glycosuria during the acute phase,[70] in a series of 100 cases of acute coronary occlusion, glycosuria was found in 10 per cent[110] The urine may contain as much as 1 per cent glucose, as well as acetone, and the blood sugar may rise as high as 300 mg per 100 cc. at the same time The glycosuria appears within 48 hours of the occlusion, and disappears within another 48 hours Carbohydrate metabolism may become disturbed during the early days of an infarction without the appearance of glycosuria or hyperglycemia.[202]

Various explanations have been proposed (*1*) In some cases there is doubtless a true latent diabetes mellitus. (*2*) Shock and pain may be responsible.[70] The occurrence of glycosuria in the absence of pain or shock would seem to make this explanation unlikely (*3*) Administration of drugs such as morphine, salicylates, or epinephrine is another suggested cause. This obviously cannot play an important role in the cases under discussion. (*4*) Increased carbon dioxide content of the blood, leading to general tissue acidosis due to decreased minute output of the heart, may be a factor of possible importance.[109] (*5*) The suggestion that absorption of the protein products of disintegration in the infarct might favor the production of epinephrine[32] seems not to be well based. (*6*) The sharp fall in blood pres-

sure may, through its effect on the carotid sinus, stimulate the production of epinephrine.[110] (7) Postmortem study of the brains of patients dying after a coronary occlusion has shown edema of the medulla and lower pons,[54] possibly this could cause the transient change in carbohydrate metabolism. (8) The acute stress of an infarction may cause increased formation of epinephrine, with resulting leukocytosis and hyperglycemia.[22]

CARDIAC ANEURYSM

A cardiac aneurysm has been defined as "a localized outpouching of the cavity of a cardiac chamber, with or without outward bulging of the external surface."[113] However, this is a pathologic, not a clinical, definition It is a common complication of major infarction, for the contractile power of the affected muscle is impaired as soon as the infarction is complete so that the injured area no longer contracts with systole and sometimes balloons outward. Considering the lack of muscle support and the pressures to which the damaged myocardium is subjected, it is remarkable that *aneurysm does not complicate every case* of severe myocardial infarction Actually, shallow depressions in the muscle wall, which are aneurysmal dilatations, are very common; but the term "aneurysm" is reserved for those cases in which there is a bulge beyond the usual cardiac contour line The aneurysm may appear as a diffuse bulge, especially if it is in the apical area, or it may be a saccular cavity large enough to be mistaken for a pulmonary tumor. Commonly, the sac has a 2 to 4 mm. thick thrombus attached to its wall; the wall itself is composed of firm, fibrous tissue which may contain a few remaining strands of muscle [41] The aneurysmal wall or the thrombus may calcify, and the overlying pericardium is often firmly attached to the heart

The incidence of aneurysm in major infarction, as reported in the literature, ranges between 6[91] and 94 per cent,[9] with 10,[134] 20,[106] [170] and 29[135] per cent as intermediate figures The most common site of aneurysm is anteriorly in the left ventricle, at or near the apex, the posterior wall is affected a third to a fourth as often, and the interventricular septum only rarely. In one large series, the apex was involved in 49 cases; the anterior wall, in 45 cases; the posterior wall, in 29 cases; and the interventricular septum, in 17 cases; the right ventricle was involved in 1 case, and the right and left ventricles combined in 3 cases.[113]

The explanation for the predominant location in the left anterior ventricular wall is (*1*) the left anterior descending artery is the one most often occluded, and (*2*) the left apex is formed by two superficial muscle layers only. Nearer the base, at least one, and possibly more, additional intermediate muscle layers provide sufficient support to prevent bulging except in the most extensive infarctions. Even at the apex, at least the thickness of one muscle must be destroyed for an aneurysm to form.[74]

Practically every case of aneurysm with infarction occurs in a large infarction. Whether mural thrombi prevent aneurysm is questionable, probably, neither a thrombus nor adhesions helps to prevent this complication.[9] An important factor in the production of aneurysm, as in cardiac rupture, is increased stress on the heart during the early stages of the attack, especially insufficient rest, systemic hypertension, and anatomic deformities of the valves or aorta [113] The average age of patients with infarction and aneurysm in one series was 65.8, but neither age nor sex seem to be determining factors [9]

CLINICAL FEATURES

Aneurysm may not be clinically recognizable for weeks, although it has been identified as early as the second day [113] Few symptoms referable to the bulge itself have been noted, with the exception of dysphagia [59] The usual picture is that of a severe infarction, often with a protracted course.

The heart sounds may be muffled and diminished, as they often are in infarction, perhaps unusually so and out of proportion to the force of the cardiac impulse Gallop rhythm is frequently present. A systolic blow can sometimes be heard over the dilated area There are no murmurs which are diagnostic of aneurysm; a diastolic murmur, first noted by Remlinger[35] in 1896, has been described—a high-pitched murmur of uncertain cause heard occasionally in cases with strongly pulsating aneurysms.[111]

Percussion may or may not reveal cardiac enlargement, and palpation usually does not disclose an unusual area of pulsation If painstaking physical examination reveals such an

area, the forceful or weak and diffuse pulsation is generally a thrust close to the apex. A feeble apical thrust in the presence of cardiac enlargement should therefore arouse suspicion of aneurysm. Unusual pulsations, only rarely conspicuous, may be noted well within or well outside the apex A recent report lists several physical signs which were found in a series of cases with ventricular aneurysms. (*1*) anomalous location of the cardiac impulse in 50 per cent of the cases; (*2*) myotonic cardiac impulse—lag of the up-and-down movement of the chest wall with the cardiac impulse—in 65 per cent of the cases; (*3*) reduplicated impulse in 20 per cent, (*4*) wavy impulse or cardiac shudder in 30 per cent; (*5*) heaving left costal margin in 10 per cent, (*6*) stony dullness over the precordium in 45 per cent, and (*7*) loud and long, musical or "cooing" systolic-diastolic murmur [131]

The electrocardiographic features are not pathognomonic. There is usually definite evidence of a large infarction In many cases of anteroapical aneurysm, persistent S–T segment elevation in the unipolar precordial leads are seen,[46, 89] there may also be a small R_1 wave and deep S_2 and S_3 waves

The diagnosis is usually made by roentgenographic examination The roentgenogram (Fig 35) or fluoroscopy will reveal a deformation of the cardiac silhouette, either diffuse or localized, except when the aneurysm is small Careful fluoroscopic examination after the eyes are well accomodated may be rewarding. a bulge with paradoxic pulsation (an outward instead of an inward thrust during systole) may be noted, in which case the diagnosis is easy, however, only a localized area of feeble pulsations or absence of pulsation may be seen. In order not to overlook posterior or basal aneurysm, the patient should be rotated slowly, the left oblique position is especially important. If the roentgenographic or fluoroscopic findings lead to suspicion of an aneurysm, the diagnosis can be definitely established by kymography or electrokymography, which easily disclose parodoxic pulsations over the aneurysm, or the absence of pulsations In most cases, however, simple fluoroscopy suffices for the diagnosis. The following roentgenographic features are useful in the diagnosis of aneurysm· (*1*) deformed contour of the left ventricle, especially in the presence of ventricular enlargement; (*2*) localized bulge inseparable from the cardiac silhoutte; (*3*) increased density or calcification of the ventricular wall; (*4*) presence of angulation or incisura, (*5*) bulging of the anterior cardiac border; (*6*) pericardial adhesions, (*7*) abnormal pulsations, or absent pulsation, in the aneurysmal zone.[113]

The over-all picture of myocardial infarction is changed surprisingly little by the aneurysm Cardiac rupture, if it occurs, does so within 3 weeks of onset of infarction; thereafter it is extremely rare even in the presence of a large aneurysm. After the first 3 weeks, the outlook is almost exactly the same as might be expected after any severe infarction, and the aneurysm, as such, may usually be disregarded in prognosis and treatment Pericarditis is more common than in the case of infarction alone, and cardiac failure will develop in a higher percentage of patients with severe infarction and aneurysm (70 per cent)

The differential diagnosis is usually not difficult. The presence of a murmur may cause suspicion of rheumatic heart disease In the presence of calcification, pericarditis with calcification, which is normally much more diffuse, must be ruled out. The bulge seen on the roentgenogram or by fluoroscopy may be confused with aortic aneurysm or pulmonary or mediastinal tumor. In most cases, careful investigation, including intravenous dye technics, will establish the diagnosis, but in rare cases, especially when dense clot fills the cavity, an accurate diagnosis may be impossible.

No special treatment is required According to Schlichter and associates,[113] prevention of aneurysmal formation may be aided by· (*1*) prohibition of early ambulation, (*2*) early and continuous anticoagulant therapy, and (*3*) a vigorous attack on early congestive failure Surgical excision of a cardiac aneurysm has been reported,[73] for a discussion of this operation, see Chapter 18

MYOCARDIAL CALCIFICATION

Calcification (Fig. 36) is an uncommon sequel of myocardial infarction [14] It may also occur in an aneurysm, and within a coronary arterial wall.[43]

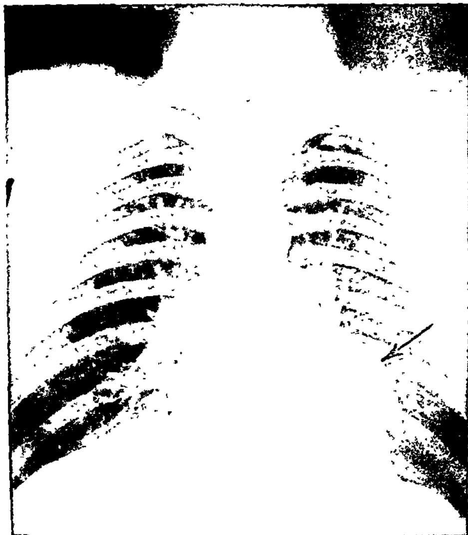


FIG 35 Cardiac aneurysm in 60 year old man who had suffered a myocardial infarction 4 years earlier. Note distinct hump interrupting the curve of the left cardiac shadow Special technics are necessary in some cases to establish that such a configuration is not the result of tumor

The existence of detectable amounts of calcium in the myocardium does not change the course of chronic coronary disease, and may be disregarded clinically. Rupture through such an area is rare [17]

The presence of calcium deposits in the ventricular wall of a middle-aged or older individual is strong evidence of old infarction, nevertheless, such deposits may also occur in the absence of coronary disease In pericarditis, the calcification is usually more diffuse, when it is localized, roentgenography will demonstrate that the deposit is on the very contour of the cardiac silhoutte, rather than in the muscle itself

AURICULAR INFARCTION

Infarction of the cardiac auricle is probably less rare than a survey of the literature would seem to indicate In 2704 consecutive autopsies, 182 cases of myocardial infarction were found, of which 31 were auricular (17 per cent) [23] In other series, 3 12 per cent of all infarcts showed auricular necrosis,[10] 7.2 per cent of infarcts were auricular; 8.5 per cent were auricular,[75] and 21 of 50 hearts studied showed auricular infarcts [136]

In most cases, the auricular infarcts are found on the right side. In the large series cited above, 27 were on the right, and only 5

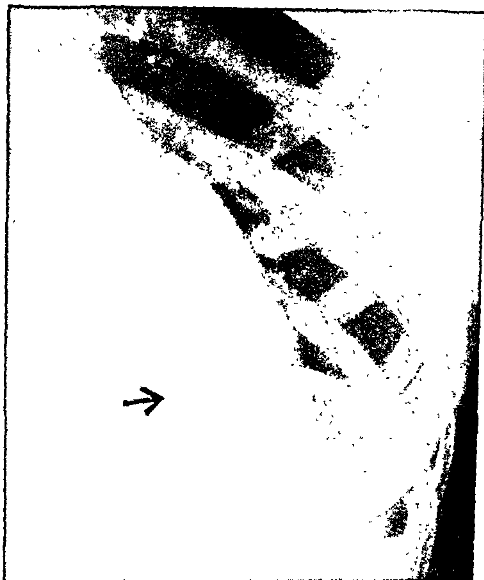


FIG 36 Calcification in an old myocardial infarct The shape of the calcified area had led to a diagnosis of pericardial cyst, this was disproved on autopsy

were on the left, most of them were in the neighborhood of the auricular appendage, only 2 were near the sinus node [34] Multiple infarcts were found in 2 cases only. Gross occlusion of an atrial artery was found in 1 case, possibly more occlusions would have been found had an injection technic been used. In 6 of the 31 cases, the only infarcts found were the auricular ones, and all 6 hearts were hypertrophied. In 22 cases the left ventricle was also infarcted. Complete or almost complete occlusion of a main coronary artery was found in 23 cases A mural thrombus tightly adherent to the underlying necrotic area was found in 26 cases

The preponderance of right-sided involvement may be explained in several ways (*1*) Since the auricles are nourished, at least in part, directly by the blood within the chamber, it is possible that the high oxygen content of the blood in the left ventricle helps to prevent tissue death. (*2*) When thrombosis occurs in the right coronary artery, the first 2 or 3 cm are generally affected, the branches which

usually supply the auricle and the auriculoventricular node are thereby cut off, although the left anterior atrial artery may also supply this area.

In 23 of the 31 cases,[31] electrocardiograms were available for study. Abnormal auricular mechanisms were found in 17 (74 per cent), in contrast to the cases of myocardial infarct without auricular involvement in which disturbed auricular rhythm was found in 8 per cent only. Auricular fibrillation was present in 9, *auricular premature beats in 4, auricular* flutter in 2, sinus arrest in 1, and wandering pacemaker in 1 The P–Q interval was depressed in 5 cases; this sign was considered of doubtful value, since it is also present in normal individuals. The changes in the electrocardiogram which auricular infarction often causes may suggest the diagnosis[55]

"Glycogenic degeneration" of the muscle, which is occasionally seen in association with ventricular infarction, is seen more often in auricular infarcts, according to one investigator.[124] In a recent report it is stated that obliterative endarteritis of the auricular coronary branches is found more often than thrombic occlusions[66]

SHOULDER-HAND SYNDROME (FROZEN SHOULDER)

Persistent pain in the left shoulder, arm, and hand, frequently found in coronary disease,[2, 56, 62, 64, 89, 126] occurs more often after frank infarction.

Some degree of pain and stiffening of one or both shoulders develops in about 15 per cent of patients[100] within a few weeks of a myocardial infarction, but pain in the hand or wrist is present in only a third of these patients Its association with heart disease may be overlooked, conversely, the pain, especially if it is on the left side, may be taken as an indication of exacerbation of the coronary disease. *The pain is sometimes especially* severe at night

The shoulder–hand syndrome makes its first appearance as a complete entity within 6 weeks of the onset of infarction, often quite early, but usually not later than 16 weeks after onset One shoulder (usually the left), and less commonly both shoulders, become painful and stiff Changes in the hands and fingers of the affected side (or bilaterally, somewhat more often than in the case of the shoulder pain) appear within a short time and consist of. (*1*) a firm, nonpitting edema of the hand and fingers; (*2*) coldness of the hand, and a color varying from erythema to different grades of cyanosis,[62] (*3*) restricted and painful finger motion; (*4*) swelling may subside, but the skin grows thicker and duller, and finger movements remain limited and *painful; (5) frequent occurrence of atrophy;* (*6*) contractions of the palmar fascia Tender areas around the shoulder joint are found frequently

Three phases of the shoulder–hand syndrome have been described[126] (*1*) Painful disability of the shoulders and/or hands, lasting 3 to 6 months, surface temperature is usually increased, and there is vasodilation. (*2*) Clearing of the features of the first phase, and the appearance of early trophic changes, venospasm, and coldness of the hand and fingers; this lasts 3 to 6 months. (*3*) Trophic changes in the hands and fingers, often with residual shoulder disability

The causes of the shoulder–hand syndrome, which also occurs in other conditions, are obscure *Various theories have been advanced,* and it is likely that several factors may be responsible Among the theories proposed are:

1 Voluntary restriction of movements of the left arm during the acute illness[76] The shoulder becomes painful on motion, then at rest, then stiff and contracted The constant shoulder pain produces continuous protective spasm of all muscles in and about the extremity, even those of the forearm and hand. This results in pain which radiates from the shoulder, like the spokes of a wheel, down the arm, up the back of the neck to the occiput, to the anterior thorax, and down the posterior axilla. To an inexperienced observer, all this suggests a neurologic disorder. According to McLaughlin,[76] the established "frozen shoulder" produces vasomotor changes, with signs of sympathetic overactivity and venous stasis

2. Pre-existing arthritis, a gouty diathesis, bursitis, or arteriosclerosis of the blood vessels of the arm.

3. Reflex vasoconstriction of the peripheral arteries resulting from cardiac pain[82]

4. Neurovascular reflex mechanism.[126] It has been postulated that impulses traveling centrally along the usual afferent pathway, which enter the widely ramifying internuncial system of neurons within the spinal cord, are the origin of reflexes responsible for the shoulder–hand syndrome. Ordinarily, incoming nerve impulses travel along specific pathways to reach predetermined efferent neurons; in the shoulder–hand syndrome, the afferent impulses set up a widespread, continuous agitation of the "internuncial pool" which stimulates anterior and lateral horn cells not ordinarily reached Peripherally, this is expressed by motor and neurovascular symptoms producing the characteristic clinical picture of the syndrome.

An analogous syndrome in the muscles of the chest wall sometimes occurs after infarction[51] (*see* Chapter 13).

TREATMENT

The simpler varieties of painful shoulder generally respond to exercises which put the shoulder muscles through a full range of motion. Although at first these exercises may cause discomfort, the patient should persist A useful exercise is leaning forward with a weight in the hand of the affected side and then swinging the weight through widening circles Heat and salicylates may sometimes be necessary

For the full-blown syndrome, cortisone or ACTH therapy is effective in some cases, and may be tried,[107] extreme caution is indicated in the presence of any degree of congestive failure. Cortisone is given in a daily dose of 200 mg until improvement is noted; thereafter, a smaller maintenance dose is given for 6 to 20 weeks The patient should be kept on a salt-poor regimen throughout the course of therapy [126] A report on cortisone therapy in 17 patients, in whom nerve block or physiotherapy had been ineffective, concludes that cortisone is the treatment of choice for the shoulder–hand syndrome [107] It gave complete relief to 5; in 8 patients there was marked improvement, and in 3 moderate improvement; only 1 patient obtained no relief

Sympathetic nerve block may be helpful,[25] and Steinbrocker[126] considers it the treatment of choice. Procaine hydrochloride, 10 cc. of a 0 5 per cent solution, for the initial infiltration, is injected into the stellate ganglion by the anterior (paratracheal) approach; *thereafter* 20 cc. are injected at 2 to 7 day intervals on an ambulatory basis. Most patients require 7 injections or less. Pain is almost invariably relieved, but there is no effect on trophic changes, once they have become established. Patients on anticoagulant therapy should not be given this treatment.

Physiotherapy and other rehabilitative measures should be employed in every case Diathermy and deep irradiation are seldom helpful [126]

To prevent the appearance of the shoulder–hand syndrome, the patient should be encouraged to move the left arm and all the joints of the upper extremities, starting as early as a day or two after onset of the infarction

PLEUROPERICARDITIS (POSTINFARCTION SYNDROME)

Dressler has recently described an infrequent complication of myocardial infarction which may follow immediately or may be delayed up to 8 weeks [25a] The syndrome consists of pain in the chest (over the precordium and left lower chest), recurring fever which may rise to 104 degrees, and either pleural or pericardial effusion or both If there is involvement of the diaphragm, there may be pain in the left shoulder In any case, the pain is cutting and is made worse by deep breathing or changes in posture. A pericardial rub is usually heard, and the ECG may show the changes of acute pericarditis in addition to those of infarction X-rays may show the presence of pericardial or pleural effusion There is a tendency to relapse (sometimes several times over a period of months), but the prognosis is good Antibiotics are of no avail, but salicylates and cortisone are effective.

The syndrome should be differentiated from extension of the infarct or pleural embolism, both of which are more common. The cause is still unknown, but it is not impossible that it may be related to the commissurotomy syndrome, found after operations on the valves of the heart, and benign idiopathic pericarditis.

RARE COMPLICATIONS OF MYOCARDIAL INFARCTION

JAUNDICE In the absence of liver or gallbladder disease, jaundice seldom complicates infarction. The jaundice is usually transient A neuroreflex mechanism has been suggested as a possible cause.[127]

OBSTRUCTION OF SUPERIOR VENA CAVA This has been mentioned as a complication in one report.[81]

SUPPURATION Abscess formation in an infarct has been reported in several cases. In 2 cases, a coagulase-positive hemolytic *Staphylococcus aureus* was found, and in 1 of them there was cardiac rupture.[128] In 2 other cases, the patients were elderly, debilitated persons.[90]

ACUTE PANCREATITIS Hemorrhage into the pancreas has been found in 4 of 115 young patients with infarction.[93] I have encountered this complication in 4 patients, 3 of whom died, the diagnosis was confirmed by autopsy

SUBACUTE BACTERIAL ENDOCARDITIS In rare cases, this may arise in a mural thrombus after infarction.[81]

MEDIASTINAL EMPHYSEMA This has been reported in 1 case, precipitated by a coughing paroxysm in acute left ventricular failure [27]

CONGENITAL CARDIAC DEFECTS Myocardial infarction has been described in association with dextrocardia; the electrocardiographic changes were mirror images of those commonly seen [85, 105] In another case, that of a 34 year old man, myocardial infarction was associated with an interventricular septal defect [132]

PREGNANCY There are reports of at least 15 cases of pregnancy in women who had had an infarction or in whom the infarction occurred during the pregnancy. In one report, 1 of 4 patients was treated satisfactorily with dicumarol for 2 months during her pregnancy, Mendelson[47] states that in a well-healed infarction, the hypervolemia of a subsequent pregnancy is not a serious problem, nor is a previous infarction an indication for interrupting the pregnancy or for cesarian section. There is also a report of a 37 year old woman who had an infarction and two subsequent attacks of decompensation during pregnancy, but who had an uneventful delivery.[47] Fresh infarction during the third trimester of pregnancy has an especially poor prognosis.[74a]

OTHER CONDITIONS Volvulus of the gallbladder[80] and Cushing's syndrome[6] have been reported in association with myocardial infarction.

CHRONIC CORONARY DISEASE

The patient who has survived an acute infarction may be considered as having chronic coronary disease for the rest of his life. However, many persons have coronary disease for months or years without ever suffering an infarction, and it is this group which may conveniently be considered at this point.

The diagnosis of chronic coronary disease can be made with reasonable clinical certainty in the presence of:

1 Definite previous infarction.

2 Angina pectoris with typical history if [illegible]

gram or a positive coronary insufficiency test

If neither of these exists, the diagnosis of chronic coronary disease (coronary sclerosis) can only be a presumptive one made largely by exclusion. Such heart disease may be present without any evidence whatsoever in a small minority of persons Some degree of coronary sclerosis may exist before it is detectable by any means we have at present; by the time it is advanced enough to present a threat to the patient, there is usually some reason to suspect heart trouble. It is well known of course that a myocardial infarct may take place in a patient who has never consulted a physician; but such cases are seldom completely "silent." The history often provides clues which have been overlooked. When complete routine physical examinations, including cardiac survey, are established, such instances will become rarer

Evidence then of coronary disease falls into two categories:

1. Clinical story. History of symptoms referable to the heart.

2. Laboratory evidence, especially the electrocardiogram

These may exist independently of one another. For example, an abnormal electrocardiogram or ballistocardiogram may be obtained in a person who seems to be in perfect health There may be a suspicious story of atypical chest pain, dyspnea, etc., in a person with no laboratory evidence of cardiac involvement. In no case, is either of these categories of evidence conclusive, they furnish the physician with valuable diagnostic data He must arrive at a presumptive diagnosis which will probably be correct. He must keep the patient under surveillance and must be prepared to change the diagnosis as new evidence is available.

1. The clinical story arouses the physician to a certain degree of suspicion.

Cardiac symptoms of any kind may be associated with coronary sclerosis sufficient to induce ischemia either temporary or permanent.

(*a*) *Atypical pain* in the chest. When chest pain is typical angina of effort (described in detail in the chapter on angina pectoris), the diagnosis is reasonably clear. Pain atypical in any way may bedevil the clinician. I can furnish no short cut to accuracy in diagnosis; the diagnostic survey should be complete, and repeated when necessary, observation should be prolonged and vigilant The patient should be reassured as much as possible.

(*b*) *Dyspnea* is a common early symptom in coronary sclerosis The sequence is coronary atheroma→myocardial fibrosis→loss of cardiac reserve. Dyspnea is of course commonly found in other types of heart disease and in many other conditions as well. Nevertheless, dyspnea unexplained in other ways should lead one to search for evidence of cardiac, especially coronary, disease.

(*c*) *Palpitations and heart consciousness* sometimes accompany heart disease. The "thumping" of extra beats or paroxysms of ectopic rhythm may be very distressing but may or may not mean cardiac trouble This group of symptoms is only a rare accompaniment of coronary disease; occasionally, however, it may be the first symptom which brings a patient to the doctor. Paroxysms of auricular fibrillation are occasionally benign but they may indicate hyperthyroidism or heart disease. Paroxysmal tachycardia, especially if supraventricular, is usually benign but every effort should be made to take an electrocardiogram during a paroxysm.

(*d*) *Heart failure* of any variety in middle-aged or older individuals should, in the absence of other forms of heart disease, be suspected as being the result of coronary sclerosis with fibrotic changes in the myocardium

(*e*) *Gastric symptoms* may be the only complaints of the patient. They are not as common or as severe as they are in acute infarction but are fairly frequent and always confusing The story is usually that of "flatulence" or "indigestion" for several weeks or months before the acute infarction. In my experience, these symptoms do not usually continuously precede an infarction for any length of time and are probably a manifestation of periods of progressive ischemia rather than of chronic ischemia or fibrosis per se. It does occasionally happen that a patient may report that his health was "always good except for a period of indigestion several years ago" Some of these may represent unrecognized acute infarction When the heart fails, gastric symptoms are of course common

2 Abnormalities in laboratory tests, especially the electrocardiogram, ballistocardiogram, or the vectorcardiogram These are discussed in other chapters.

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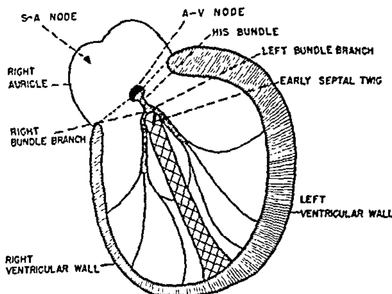


FIG 37 Cardiac structures important in electrocardiography (From Wolff[92] [Chapter 10])

diagnosis of infarction was missed in many cases Addition of 1 precordial lead at the apex *increased the accuracy of diagnosis;* the addition of 2 or 3 more precordial leads, so that the 6 conventional precordial leads became the rule, brought a corresponding *increase in diagnostic accuracy* and major infarction is now being missed in fewer than 5 per cent of cases When fewer than 12 leads are used, the diagnosis may be missed in about 25 per cent of cases.

Tracings taken from the body surface may not reveal minor degrees of injury, but do show changes if transmural or subtransmural lesions are present.[17] Were it possible to take epicardial and myocardial tracings in man, as is done in animals, even the smallest areas of infarction would be detected

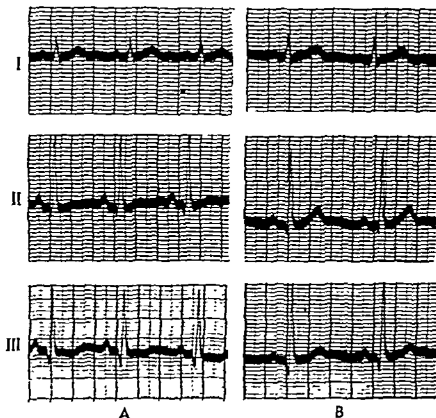


FIG 39 Electrocardiographic changes with shift in body position in a healthy 12 year old girl A, Seated, B, supine (From Graybiel et al[25])

COMPLICATING DISEASE Disease complicating myocardial infarction causes the most serious *difficulties in interpreting* the ECG. The patient with an infarction may also be suffering from noncoronary heart disease, *e g*, hypertensive or valvular heart disease, which effects the ECG. Or the patient may have earlier coronary disease or an old infarction. The changes which these cause in the ECG are most perplexing when one is attempting to diagnose a fresh infarction, and serial studies become an absolute necessity in such cases. Despite such studies, it is sometimes impossible to determine accurately the site of the infarction, although its presence is beyond doubt.

NORMAL ELECTROCARDIOGRAPHIC VARIATIONS These are common, and may lead the unwary to a mistaken diagnosis of infarction. If the follow-up tracings are then *taken with the patient in a different position,* or the precordial leads are shifted even a little, the error may be sustained An ECG taken in various phases of the respiratory cycle may show variations which might be considered abnormal (Fig. 40)

TABLE 16. DETERMINATION OF ERRORS RESULTING FROM MISAPPLICATION OF LIMB LEAD ELECTRODES[21]

	Arm connections reversed	*Left arm and left leg connections* reversed*	*Right arm and left leg connections reversed*	*Clockwise rotation all lead connections*	*Counter-clockwise rotation all lead connections*
Polarity strip 1	↓	↑	↓	↑	↓
Polarity strip 2	↑	↑	↓	↓	↓
Polarity strip 3	↑	↓	↓	↓	↑

* *Most easily overlooked because Lead 3 is often normally inverted*
↓ Strip or "lead" "upsidedown"
↑ Strip or "lead" "upright."

PREMONITORY PHASE AND ATYPICAL INFARCTION The premonitory phase of coronary occlusion commonly precedes myocardial infarction and may represent a reversible stage. In many cases, the ECG is normal, but depression of the RS–T segment and/or T wave changes may appear; in exceptional cases, the RS–T segment is elevated. The changes are those of subendocardial ischemia, perhaps necrosis[27]

Routine electrocardiography may fail to reveal atypical infarcts, small intramural infarcts (*see* Figs 16 and 17, Chapter 1), and small infarcts in ususual sites.

OTHER DISEASE A number of conditions which may cause electrocardiographic changes resembling those of infarction are listed in Table 20, Chapter 13

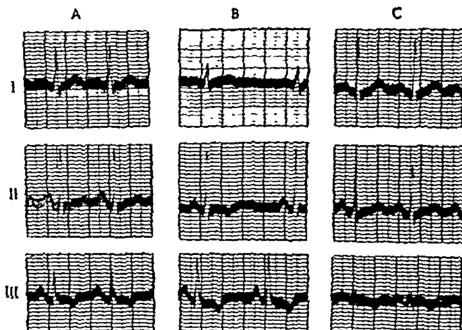


FIG 40 Electrociographic changes associated with changes in respiration A, Control, B, full inspiration; C, full expiration (From Graybiel et al[21]

TECHNICAL ERRORS Misapplication of electrodes (Table 16), with a resulting erroneous tracing, occasionally results in a mistaken diagnosis of infarction.

ELECTROCARDIOGRAPHIC STAGES OF MYOCARDIAL INFARCTION[30]

One classification of the changes of myocardial infarction as they appear on the ECG is helpful to a limited extent. *Stage 1* is that of ischemia, and is characterized by T wave changes. *Stage 2* is that of injury, and is characterized by displacement of the S-T interval. *Stage 3* is that of necrosis and is characterized by changes of the QRS complex.

It must be borne in mind that the categories of this classification denote electrocardiographic changes which correlate only roughly with clinical events or demonstrable anatomic changes (Fig 41) The nomenclature given, although based on sound experimental evidence, is too simple for the very complex changes that occur in the human heart during the entire process of coronary failure. However, if it is recognized that the classification is merely a convention and is applied to the problems of infarction in man with caution, it can be useful.

In general, all three electrocardiographic changes occur in major infarction, experimental or spontaneous, and all three should be seen on the ECG for the diagnosis to be made with reasonable certainty. In minor degrees of infarction, or in coronary insufficiency without evident tissue necrosis, one or two of the changes may be seen alone. In such cases, Stage 1 corresponds approximately with the more benign forms of damage, Stage 3 with the most severe But in every case all the evidence, electrocardiographic and clinical, must be considered together in order to obtain a true picture of the case. It is noteworthy that the three stages do not follow each other in sequence in major infarction, and that T wave inversion is usually the last change to appear, not the first

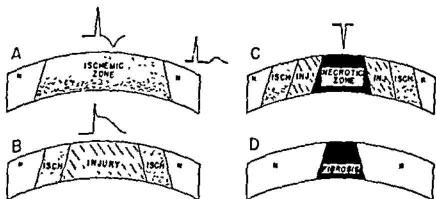


FIG 41 Successive stages in development of transmural myocardial infarction after coronary artery occlusion A, Stage of ischemia, normal QRS complexes followed by characteristic T wave inversion in leads from vicinity of epicardial surface of ischemic zone, B, stage of injury central part of involved muscle shows injury effects and enlarges at expense of ischemic zone, upward RS-T displacement in leads from vicinity of epicardial surface of injured zone C, stage of necrosis, muscle in central portion has become necrotic, and since dead muscle produces no electric forces it merely acts as a conductor and transmits the cavity potentials through to epicardial surface, QS deflections in leads from vicinity of epicardial surface of this area, injured zone is rapidly disappearing and ischemic zone is much smaller, D, old healed infarct in which fibrotic scar has contracted, QS deflections will still be recorded from epicardial surface of this area, ventricular complexes from adjacent areas will be essentially normal or modified (N, normal muscle) (From Yater The Fundamentals of Internal Medicine, 4th ed, 1954 Courtesy of Appleton-Century-Crofts, Inc)

STAGE 1: ISCHEMIA As used in electrocardiography, the term "ischemia" applies to an electrical field abnormality. When it occurs alone, and not as part of the sequence of stages 1 through 3, it usually represents a relatively benign form of coronary insufficiency, and not major infarction. Nevertheless, *exceptions occur often enough to make wariness advisable*, catastrophic infarction may develop in such cases, or the patient may die suddenly

The T wave represents the repolarization or rebuilding of electric charges, and is therefore essentially a different biophysical process from that responsible for the QRS complex

Modifications in the T wave m… be expected in some patients… complex is unaffected T wave… may be caused by a variety of c… than coronary disease, all of… considered in the differential… Chapter 13).

The vector QRS–T angle is… is fairly constant By means o… graphy, it is possible to differ… T wave changes due to the… and those due to impaired c… tion: in the former, the Q… normal, in the latter, the angle… ischemic site is in the epicard… is often the case in the early…

due to some other condition, or may even be … normal phenomenon,[12] rarely, such prolonged elevation is caused by severe myocardial infarction, usually in association with ventricular aneurysm

The other causes of S–T deviation are:

1 Digitalis effect, in which the shift is opposite in direction to the QRS vector, it therefore appears as a sagging of the baseline.

2 Ventricular strain, in which the change is due to a T wave change and is not the result of injury Both the S–T and T vectors … about 180° from the QRS vector, and the electrocardiographic changes are easily distinguished from the "injury" pattern when analyzed vectorcardiographically

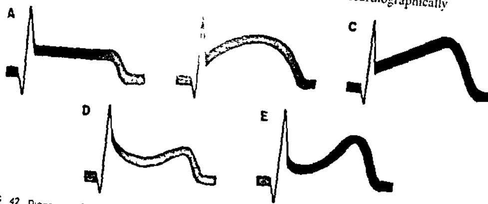


FIG 42 Diagrams of abnormal … ments A, Plateau RS-T B, dome … RS-T C … liquely elevated RS-T, D, crescent RS-T E … voted RS-T with normal downward convexity (From Goldberger [25])

tion, the T wave points away from the involved area, if the side is subendocardial the vector points toward the ischemic area

STAGE 2 INJURY Deviation of the S–T segment is usually interpreted as a sign of severer injury than that indicated by T wave change, Nevertheless, although it is seen mainly in association with infarction it cannot by itself, be considered as proof of infarction The presence of such deviation should lead to serial electrocardiography and close extended observation of the patient The cause of the S–T deviation in acute infarction is not known precisely, the currently held theories are discussed by Barker · S T deviation as a rule elevation in the leads which will eventually show deep Q waves, generally lasts some hours to some weeks The different forms of S–T elevation are shown in Figure 42 When this abnormality lasts for months, it may be

3 Bundle-branch block, in which condition the S–T and T vectors are roughly parallel to each other, as in ventricular strain Bundle-branch block complicated by acute infarction is considered on page 156.

4 Tachycardia, in which the S–T segment may appear to be abnormal, due to shortening of the Q–T segment, so that T forces may appear during the S–T interval

5 Normal persons with abnormally large T waves may show a shift in the S–T segment of as much as 2 mm The segment is occasionally elevated, and exercise causes it to revert to normal The theory which best explains this segment elevation is that early repolarization occurs in the subepicardial myocardium before the activation, or depolarization, of the whole ventricle has been completed

No attempt should be made to correlate the S–T elevation with the injury's severity or with the prognosis. "Wild-looking" S T …

placement may be seen in patients whose illness is running a benign course; conversely, slight or no displacement does not necessarily mean slight injury Nevertheless, the longer the displacement lasts, the more likely is the cardiac lesion to be severe. Furthermore, renewed displacement after a return to the base line usually indicates the infarct's extension. The electrocardiographic evidence of injury may be followed by signs of healing or of additional infarction, in which case changes in the QRS complex appear

STAGE 3 NECROSIS In "necrosis" or focal death of tissue, i e, true infarction, the necrotic tissue is unable to produce electric forces but can act as an electric conductor. The QRS forces from other parts of the ventricle are unopposed during electric discharge until the discharging process is completed in the subendocardium and has spread into the other layers The electric forces therefore point away from the dead zone

On the ECG this is represented by a Q wave of 0 04 sec or longer, or, in some cases, especially in the later stages, by the diminution or absence of an R wave normally expected in that location The significance of Q waves of 0.03 sec or less is not as sinister

Of all the changes in the ECG in infarction, those of the QRS complex last longest In the course of months, and much more rarely of years, the necrotic zone may shrink sufficiently to cause disappearance of the Q deflection from some or all of the leads In some cases, a new, posterior wall infarction may obliterate the Q wave deflections of an old infarction, islands of living tissue in the old infarcted area produce positive voltages strong enough to remove the old Q waves when the posterior opposing forces are eliminated

The corrected Q–T interval is somewhat elevated in acute infarction (average, 0.448 sec, in contrast to a normal of 0.397 sec.), but reverts to normal within 1 month[31]

ELECTROCARDIOGRAPHIC LOCALIZATION OF INFARCTS

The attempt to determine the exact site of an infarct is useful, and sometimes successful, but it is by no means an indispensable procedure. The correct diagnosis of infarction is far more important than its accurate localization; the latter adds little to our knowledge of the case or its outlook Nevertheless, in a large number of cases of first infarction, and possibly in over half the cases of subsequent infarction, the site of the infarct can be determined. This may be valuable information in the patient's history, particularly if the original ECG's are unavailable How often, when treating an acutely ill patient, would we like to know whether there had been an earlier infarction and its location. Table 17 summarizes the principal electrocardiographic changes in acute myocardial infarction

ANTERIOR WALL INFARCTION

The typical ECG in a completed, large, anterior wall infarction shows a deep Q wave and an inverted T wave in lead I, and usually in leads II and aV_L as well. The same changes also appear in some or all of the precordial leads

In the typically involuting case, there is an

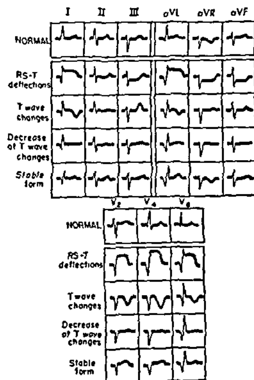


FIG 43 Successive electrocardiographic patterns after anterior wall infarction (From Goldberger[19])

TABLE 17. ELECTROCARDIOGRAPHIC CHANGES IN ACUTE MYOCARDIAL INFARCTION[82]

Lead	*Site of Infarction*						
	Antero-septal	*Antero-lateral*	*Extensive Anterior*	*Posterior*	*Postero-lateral*	*High Antero-lateral*	*High Postero-lateral*
V_E	+	−	+	+	−		
V_1	+	−	+	−	−		
V_2	+	−	+	−	−		
V_3	+		+	−	−		
V_4		+	+				
V_5		+	+		+		
V_6		+	+		+		
aV_R			−				
aV_L		+	+	−	+	+	+
aV_F		−	−	+	+	−	−
E_v				+	+		
I		+	+	−	+	+	+
II				+	+		
III		−	−	+	+	−	−
Higher interspaces, anterior thorax		+	+		+	+	
Higher aspects, left back or axilla							+

E_v, Esophageal leads at ventricular levels
+, Abnormal Q or QS deflections, abnormal upward displacement of S–T segments, and characteristic T wave changes
−, Reciprocal changes
V_E, V lead from tip of ensiform process of the sternum (Wilson)

orderly sequence of changes which may be followed at the bedside, if tracings are obtained early and often enough (Fig. 43). The rate of the changes in the ECG varies from patient to patient, in some being completed in hours and in others after days. This, combined with the fact that the first ECG may be taken too early to show changes or when the infarction is in a late stage of development makes the physician's task harder but not impossible. The difficulties merely reflect the lack of absolute correlation between the structural and chemical changes in the heart on the one hand and the clinical picture on the other—the correlation is close but not complete.

The very earliest abnormalities, as a rule missed in everyday practice, are occasionally observed in the "premonitory" stage or in the early hours of subendocardial involvement, at which time actual tissue death has not yet occurred. The T waves are smaller than normal in lead I, and sometimes in lead II and the precordial leads, more rarely, they may be larger. The S-T segment may be slightly depressed in these leads. In the absence of earlier ECG's obtained when the patient was in good health, the change in T wave ampli-

tude may be overlooked In any case, a T_1 wave which is low compared to the R wave in a person with normal blood pressure suffering from cardiac pain should suggest early anterior wall infarction This is especially true if there are inverted or isoelectric T waves in leads V_5 and V_6.[17]

In the next stage, usually the first noted *in hospital practice, the S–T segments are* displaced upward, with an upward convexity of the curve, in the characteristic leads: I, II, aV_L, and the precordial leads. An R wave is generally present, and the S–T segment takes off from its descending limb, sometimes near the very top, giving the complex a most bizarre appearance The T wave in most cases is somewhat distorted The reciprocal changes usually *consist of depression of the S–T* segments in leads III and aV_F

In the following stage, Q waves appear and alterations in the T waves in some or all of the affected leads The Q waves are more than 0 04 sec wide, and the height of the R wave is decreased In some cases, the R wave is absent, and a QS complex results, *i e.*, a downward deflection only The S–T segments are not as high as in the preceding stage, and the T waves become deeply inverted, with a sharp apex The portion of the T wave before the apex is "coved," *i e*, with a curve in which there is an upward convexity, the second half of the wave, *beyond the apex, is usually of* about the same length, with a similar, not quite so marked, upward bowing

Unipolar limb leads contribute little of value to the diagnosis of anterior wall lesions The changes in aV_L are usually the same as in lead I, and often the two leads look exactly alike.

Two points are worth emphasis (*1*) The electrocardiographic *pattern is not static but* changing, and the changing picture is a more important indication of recent infarction than is the appearance of any one tracing (*2*) The ECG in recent major infarction is practically never normal, and may be confusing When the ECG remains entirely normal on thorough and repeated study, the diagnosis of fresh, major infarction cannot be considered as *completely established*

It is of inestimable value to have an ECG taken before the attack, preferably as recently as possible, when the question of infarction arises For this reason, taking an ECG should become part of the routine physical examination of any individual over the age of 30, and the tracings, even those considered normal, should be preserved.

Usually, it takes 4 to 12 weeks for the ECG to become completely stabilized; rarely, the process may require several months. In my *experience, no signs of healing appear after* 6 months, although such instances have been described by others.

The electrocardiographic landmarks of old infarction—Q wave, low or absent R wave, low, isoelectric or inverted T wave, and malformation of QRS complex—may appear singly or in any combination in one or more of leads I, II, and aV_L, or the precordial leads. *T wave inversion in the V leads is found in* 10 per cent of normal Negroes, the inversion is exaggerated by hyperventilation and abolished by potassium salts or by Pro-Banthine [56]

VARIATIONS IN PATTERN OF ANTERIOR INFARCTION

The precordial leads are of diagnostic importance in interpreting variations from the *typical pattern However, it should not be* assumed that the unipolar or other precordial leads reflect in absolute fashion what is occurring in the myocardium directly under the exploring electrode, too many factors are involved in the resultant tracing from any location on the thoracic wall The information provided by these leads, though of only roughly approximate value, is useful for localizing the lesion The precordial leads in persons with small chests are close to each other and to the heart, a small infarct can therefore cause abnormalities in more derivations from these leads than a similar infarct *in persons of larger body build The size of* the infarct is probably overestimated in small patients and underestimated in large ones Furthermore, the more the infarct differs in shape, size, or position from the typical ones described above, the less accurate becomes the electrocardiographic localization.

Anteroseptal Infarct (Fig 44). In this type of infarct, which is probably the most common variety, the precordial leads are of the greatest value, while the limb leads show few changes Leads I, II, and III are often within normal limits QRS changes may occur in

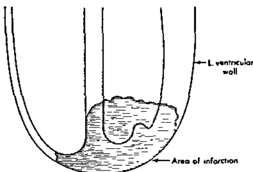


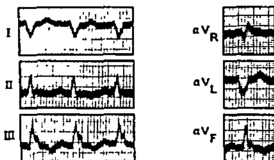
FIG 44 Anteroseptal infarction.

leads V_1, V_2, and V_3, and sometimes in V_4. Deviation of the S–T segment and T wave inversion may appear as far to the left as lead V_6. The appearance of diagnostic changes in the QRS complex or in the T wave in the limb leads should suggest the possibility of a complicating high anterolateral infarct

SEPTAL INFARCT[53] This is often associated with cardiac irregularities and conduction defects (Fig. 45). Useful criteria for the electrocardiographic diagnosis of this type of infarction are: a combination of a Q_3T_3 pattern (posterior wall involvement, as shown in the limb leads), and Q and T wave changes in the right-sided precordial leads (V_1 to V_4)[60] These criteria, although satisfactory, fail in about half the cases In one series of 11 cases of septal infarction proved at autopsy, these changes were found in only 4 cases, frank bundle-branch block was found in 6 cases (4 left, 2 right)[47]

A recent report offers improved criteria and a useful shorthand method for describing changes in the main complex.[67] In this nomenclature, a capital letter denotes a large deflection in the main complex (QRS), a small letter a small deflection Thus, QrS denotes large Q and S waves and a small R wave; rS, absence of Q wave, small R and deep S waves.

The criteria for massive septal infarction are (*1*) in the absence of conduction defects, QS in leads V_3 and V_4, and sometimes in V_1



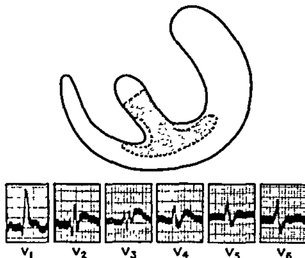


FIG 45 Electrocardiograms from a case of septal infarction From Hill

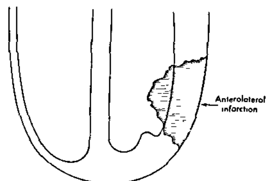


FIG 46 Anterolateral infarction

through V_4, (2) when complicated by left bundle-branch block, QrS in leads V_3 and V_4, (3) when complicated by right bundle-branch block, Q waves in the right precordial leads or in V_3 and V_4. For infarction of the inferior third of the septum, with its high incidence of complete or incomplete bundle-branch block, *the criteria are in the presence of left bundle-branch block*, possible qRs in leads V_3 and V_4 and Q waves in leads oriented to the free wall of the left ventricle. In infarction of the superior third of the septum, bundle-branch block was found in all cases but no typical ECG. In septal fibrosis, there was no characteristic ECG, but the fibrosis could be inferred from the presence of conduction defects

ANTEROLATERAL INFARCT (Fig 46) This type is somewhat less common than anteroseptal infarction but is a more extensive process, usually embracing a large part of the anterior surface of the distal portion of the left ventricle, the anterior portion of the septum, and, rarely, extending to the right ventricle. The occlusion is generally in the anterior descending artery

The electrocardiographic changes vary considerably, depending on the extent of the lesion. Deep Q waves and inverted T waves *in precordial leads 4 through 6* are diagnostic, similar changes often occur in lead aV_L, much less often in aV_R (Fig. 47). Q waves and inverted T waves are found in about half the cases in lead I, and much less commonly in lead II of the limb leads. Changes in the limb leads are nonspecific for infarction in about half the cases in which they occur.[62]

The reciprocal changes in early infarction are depressions of the S–T segment in leads V_1 through V_3 and perhaps in leads III and aV_F. Later in the course, there may be high R waves and tall, pointed T waves in the right-sided precordial leads

The late landmarks of old anterolateral infarction are deflections of Q waves and inversion of T waves in leads V_4 to V_6, and aV_L.

The QRS complex in the precordial leads deserves particular attention in anterior wall infarctions, especially the anterolateral variety. In the normal ECG, the height of the R waves increases progressively as the precordial leads pass from right to left; if there is no increase in height, anterior wall infarction should be *suspected. In rare cases of anterior infarction*, an initial R wave may appear in place of an

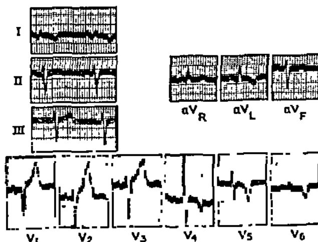


FIG 47. *Electrocardiogram from case of anterolateral infarction* (From Hill[25])

expected Q wave, for example, in V_5 and V_6 in anterolateral infarction This may be caused by:[52] (*1*) Displacement of the transitional zone to the left, due to heart shift to the left in intrathoracic disease, or to right ventricular enlargement, or to clockwise rotation of the heart, or to backward rotation of the apex about the transverse axis of the heart (*2*) Left bundle-branch block. (*3*) Taking an ECG before myocardial changes have obliterated the response of the activating impulse. (*4*) Patchy infarction, with islands of living muscle. (*5*) Localized anterolateral infarction complicated by extensive infarction elsewhere in the left ventricle (*6*) Infarction of the left side of the septum

LATERAL WALL INFARCT[55] Although infarction confined largely or exclusively to the lateral wall of the left ventricle is infrequent, it is probably more common than was once believed A characteristic electrocardiographic pattern has been described· depression of the S–T segment in leads I and II, and particularly in leads from the left side of the precordium[95] Other investigators deny the existence of a typical pattern[76]

Myers and co-workers[71] classify lateral infarcts into three categories High lateral, low lateral, and small midlateral.

1 High lateral infarcts involve principally the basal half of the heart, a Q wave in aV_L which is not necessarily duplicated in lead I may suggest the existence of this lesion The changes in the high precordial leads may be decisive These leads should be taken at the intersection of a horizontal line through the sternal end of the third intercostal space with vertical lines in the plane of precordial positions 3 through 6

2 Low lateral infarcts are confined to the apical third of the lateral wall, abnormal Q waves are usually present in leads V_5, V_6, and/or aV_L

3 Small midlateral infarcts are rare In the 2 cases of the series reported by Myers and associates, the characteristic pattern of lateral wall infarction (depression of S-T segment in leads I and II) was found

APICAL INFARCT Apex alone is an unusual site of infarction, and electrocardiographic diagnosis is difficult In a case confirmed by autopsy, that of a 66 year old woman, the changes were[2] (*1*) Q waves and upward deflection of the S–T segment in leads II, III, and aV_F; (*2*) Q waves in leads V_3 and V_4, less marked in other precordial leads, and (*3*) downward displacement of the S–T segment in lead aV_L.

RIGHT VENTRICULAR INFARCT This is found as an extension of infarction elsewhere. There is no characteristic pattern in the ECG.[53]

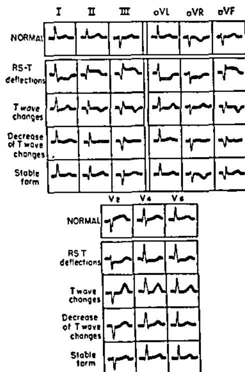


FIG 48 Successive electrocardiographic patterns after posterior infarction (From Goldberger[19])

POSTERIOR WALL INFARCTION

(Fig 48) Lesions of the posterior wall affect leads II, III, and aV_F The involutionary changes are those described for lead I in anterior wall infarction The reciprocal changes, if there are any, are found in lead I, somewhat less often in lead aV_L, and still less often in lead II Often, the S–T segment sags in leads V_1, V_2, and V_3; in addition, there may be an R wave and a high, sharp T wave in these leads and in lead aV_T Diagnosis during the acute stage is usually not difficult, but in chronic coronary disease or in old infarction, in which there are no shifting

electrocardiographic patterns, the diagnosis may be extremely difficult. The difficulty arises from the fact that a Q wave and an inverted T wave in lead III is normally present in some individuals

The differential diagnosis is aided, if the following points are remembered

1 The Q wave in lead III is wider than 0 03 sec in recent or old infarction, this is more important than the depth of the Q wave

2 Changes in the Q and T waves in lead II similar to those of lead III are a definite indication of coronary disease

3 Changes in the Q and T waves of lead aV_F similar to those of lead III, are an almost certain sign of infarction False negatives (absence of Q wave in lead aV_F, Qs and infarction present) may occur, especially if the infarct is high on the posterior wall or if the S–T segment is elevated False positives may occur occasionally The Q wave which is normally present is small and narrow Thus, in a series of 55 cases with normal Q waves, QaV_F was 25 per cent or more of R in only 3 cases, and in none did it exceed 0 03 sec in width [98] A Q wave may appear normally in lead aV_F in the supine patient and disappear when he sits up [70] In general, this lead is more reliable than lead III in detecting posterior wall infarction A Q–R ratio of over 25 per cent in lead aV_F is stated to be the best of several criteria for the diagnosis of infarction in this location, but is still subject to considerable error [60] Correlation of the changes in lead aV_F and of the autopsy findings in a large series of cases led Myers and coworkers[54] to formulate the following criteria for the diagnosis of posterior wall infarction

1 Vertical, semivertical, or intermediate position of heart (lead aV_I shows relatively small R and deep S waves, and an equiphasic RS complex or multiphasic QRS of low voltage; R wave usually prominent in aV_F) QR complexes of 0.5 millivolt or more, with a Q wave of 0 03 sec or more from onset to nadir and a Q–R ratio of over 25 per cent are indicative of posterior wall infarction Borderline complexes are considered positive if: (*1*) the Q wave is 0 04 sec or more from onset to nadir; (*2*) the Q wave is followed by an abnormally prolonged, notched, or coarsely slurred upstroke, (*3*) the tracing is taken early and shows classic S–T displacement; or (*4*) available earlier tracings show normal patterns

2. Horizontal to semihorizontal position of the heart (prominent R wave in lead aV_I, small R and deep S waves in lead aV_F, or an *equiphasic RS complex, or an RSR pattern,* or a QS pattern not due to posterior wall infarction) In a series of 35 cases, lead aV_F had a small R wave and a deep S wave *in no way suggestive of posterior infarction in* 22 cases. A Q wave may be seen if the infarction continues into the septum, if the infarction is acute, changes in the S–T seg*ment of the complex are characteristic The* QS deflection in late or healed infarction may be hard to distinguish from a normal variant Lead aV_FR should be taken during deep *respiration in the erect position If an R wave* appears, the pattern is probably normal, if a triphasic complex (small Q and R waves, deep S waves) appears, or a deeper, wider Q wave, infarction is probably present.

A simple and reliable test is the use of lead IIIR (lead III repeated while the patient is holding a deep breath) [13] A normal Q wave in lead III will diminish, disappear, or become an R wave In myocardial infarction, the Q wave will remain stationary or become deeper. According to Evans,[13] the following criteria in lead IIIR are diagnostic. In the normal heart, the Q wave is never over 2mm in depth, the Q wave does not deepen as compared to lead III nor does it appear if absent in lead III, a T wave upright in lead III does not diminish, the S–T segment is not depressed In left ventricular preponderance, depression of the T wave or S–T segment indicates coronary disease In posterolateral infarction, *there may be no Q wave in lead* III, but the S–T segment and the T wave in lead IIIR may be depressed In postero-inferior infarction, in which there is a Q_3T_3 *pattern, there are no changes in lead IIIR* Lowering of the S–T segment or the T waves in lead IIIR may be the only suggestion of earlier infarction

On the basis of over 2000 tracings, I have been able to confirm Evans' observations, with some minor modifications· In posterior wall lesions, the Q wave is often deeper in lead IIIR than in lead III There seem to be no false positives, false negatives occur in

at least 5 per cent of cases—Q waves which revert toward normal despite the known existence of old infarction Nevertheless, lead IIIR is valuable, and I use it routinely. It should be used whenever there is a Q wave in lead III The same maneuver may be tried for lead aV_F (lead aV_FR)

The use of leads II, aV_F, and IIIR will resolve almost all doubts, and esophageal leads may be used if some question still remains There are no false positive Q waves in these leads, but in general this method is no better than the others, especially the use of aV_F.[56, 71]

Despite expert electrocardiography, the diagnosis may still be missed in acute posterior wall infarction, especially if there is left bundle branch block or concomitant acute anterior wall infarction, or if the infarction is located high on the posterior wall It is noteworthy that the electrocardiographic features of an old anterior wall infarct may disappear with the appearance of a fresh posterior wall infarction and thus obscure the existence of a prior infarction

In situations in which diagnosis is difficult, posterior wall infarction should be considered if [94] (*1*) in acute anterior infarction there are no, or poorly developed, reciprocal changes, (*2*) signs of bundle-branch block or severe auriculoventricular block suddenly appear on the ECG of acute anterior infarction, and (*3*) the reciprocal and only changes are S–T segment depression, or tall R and T waves in the right-sided recordial leads The last are particularly apt to occur with high posterior wall infarcts

In summary, the diagnosis of posterior wall infarction is less easy than it seems The changing pattern in acute infarction is a considerable help, but as the infarct ages the diagnosis grows increasingly hazardous, and the percentage of error in establishing the presence of old posterior wall damage is still high

VARIATIONS IN PATTERN OF POSTERIOR INFARCTION

The characteristic pattern of a massive, major infarction in the posterior wall presents no diagnostic difficulties But unusual factors, such as old infarction, small size of infarct, or uncommon location of infarct, may make the diagnosis much harder, especially when the heart is in the horizontal position The posterior surface of the heart is relatively inaccessible to the exploring precordial electrodes, and despite every refinement in technic the accurate localization of the infarct may be missed, although the presence of myocardial infarction is quite evident clinically. However, the diagnosis of infarction is incomparably more important than its precise localization While every advance in technic aids the anatomic diagnosis, we are still far from perfection.

POSTEROLATERAL INFARCT Changes appear in leads III and aV_L, and similar changes in V_6 and sometimes in V_5. Transient T wave inversion in leads V_5 and V_6 appears occasionally in the early stages of posterior wall infarction, this indication of temporary ischemia in the lateral wall disappears as the involved area contracts to its final size

HIGH POSTEROLATERAL INFARCT The limb leads in this rare variety of infarct resemble those of the high anterolateral infarct Lead aV_F is not affected, but abnormal variations in potential are transmitted to the left arm (aV_L) With a large infarct, the changes are [65] (*1*) signs of infarction in leads I and aV_L, (*2*) a predominant R wave in lead V_1, (*3*) absence of a definite transitional zone in the precordial leads, (*4*) high, upright T waves in two or more V leads, (*5*) in the acute stage, depression of the S–T segment in the V leads V_5 and V_6 often overlying the infarct In the presence of considerable ventricular hypertrophy, depression of the S–T segment in the precordial leads (farther to the right than in left ventricular hypertrophy alone), and reduced R waves (often with splintering) in leads I and aV_L are seen

Leads V_7 through V_9 should be taken when this lesion is suspected,[65] V_7 is taken at the left posterior axillary line, V_8 at the subscapular line, and V_9 at the paravertebral line, all on the same level as leads V_5 and V_6 (the level of the fifth left interspace at its junction with the midclavicular line) Normally, these leads show an upright P wave, a small, narrow Q wave, a moderate R wave, and an upright T wave Still higher leads may be taken from points vertically above V_7 through V_9 at the

horizontal level of the third interspace at its junction with the sternum; these leads are similar to leads V_7 through V_9, in form but lower in voltage. When the posterior wall infarct is confined to the diaphragmatic surface, these high leads are normal in form.

POSTEROSEPTAL INFARCT In this lesion, the changes described as typical of posterior infarction are found, but they extend for a variable distance into the posterior part of the interventricular septum and often to the nearby free wall of the right ventricle The same changes are noted in leads II, III, and aV_F, and there are diagnostic changes in lead V_E [2]

COMBINED INFARCTS[2]

Infarcts superimposed on one another may confuse the clinical, and especially the electrocardiographic, picture A new infarct may develop on the site of an old one, and a recent infarct may be complicated by extension or fresh necrosis elsewhere in the myocardium There are no rules for identifying these changes The sequence of events may be clearly seen if careful serial ECG's are done, and particularly if earlier tracings are available Sometimes the fresh infarct obliterates all trace of the earlier one (Fig 74, Chapter 11) Large infarcts involving more than one surface of the heart or extending into the septum may give the picture of a combination of infarcts, in the absence of serial studies, a definite diagnosis of the kind of infarct may be impossible

INFARCTION COMPLICATED BY BUNDLE-BRANCH BLOCK[10]

Most bundle-branch blocks are the result of chronic coronary narrowing and the consequent myocardial fibrosis. Such block may occur for the first time during the course of an acute infarction[45] and make the diagnosis of acute infarction more difficult, since the electrocardiographic abnormalities may be due to the conduction defect rather than to the infarctive process.

RIGHT BUNDLE-BRANCH BLOCK It is reasonably easy to establish the existence of coronary disease in the presence of right bundle-branch block, because the changes in potentials in the left ventricle are undisturbed In general, the Q waves appear as usual; the changes in the S–T segment and T wave inversions may be somewhat modified.

1 In anterior infarction (Fig 49), the standard (I, II, and III) and unipolar limb leads are normal The main changes are seen in the right-sided precordial leads: disappearance of the R wave in leads V_1 and V_2, and the usual elevations of the S–T segment; possible appearance of a Q wave, inversion of the T wave. The landmarks of old infarction are Q waves in leads V_1 and V_2 The ECG resembles that of an anteroseptal infarction, but in the presence of right bundle-branch block this localization cannot be made with assurance The first precordial lead (V_1 or CR_1) may be the only one to show the changes of infarction [49]

2. In posterior infarction (Fig 50) there are the usual changes in leads II, III, and aV_F The precordial leads show no abnormalities, as a rule [51]

3 In Wilson (wide-S) block, the QRS complex is at least 0 11 sec wide with a slender R, and a wide, slurred R wave in lead I or II, in the right ventricular leads there is a secondary R wave with a delay of at least 0 07 sec Most observers have long held that this is a relatively benign form of block, and that it may be unassociated with organic heart disease, especially in persons under the age of 40 Papp and Smith,[50] however, conclude that Wilson block without organic heart disease is rare When this block is due to infarction, it is more likely to be anteroseptal than posterior wall infarction When the block appears in posterior wall infarction, the lesion is usually extensive, especially if there is associated auriculoventricular block.

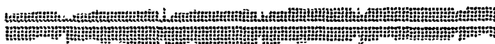
Anterior infarction may modify the pattern of the Wilson variety of right bundle branch block the diminution of left ventricular potentials may transform it into the classic pattern of right bundle branch block Conversely, right bundle branch block may also modify the signs of anteroseptal infarction by obliterating the RS-T elevation of acute injury Acute posterior infarction may not show in Wilson block with a horizontal heart, the additional A-V block with clinical signs of infarction is here diagnostic [48]

LEFT BUNDLE-BRANCH BLOCK This type of block makes the diagnosis of myo-

I

a'

aV_L



a'



V4 V5 V6

FIG 49 Electrocardiogram from case of anterior myocardial infarction and right bundle branch block (From Graybiel et al.[21])

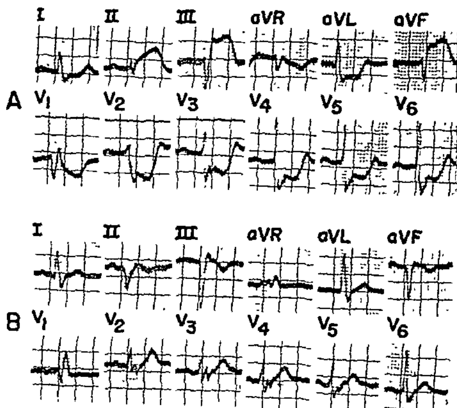


FIG 50 Electrocardiogram from case of posterior myocardial infarction and right bundle-branch block A, Few hours after onset B, three weeks later (From Graybiel et al [21])

cardial infarction difficult, in 52 per cent of cases in *one series the diagnosis was* impossible because there were no electrocardiographic signs of infarction [50] According to Barker [2]

When intraventricular conduction is normal, those electrodes which are placed adjacent to the necrotic zone of an infarct in the free wall of the left ventricle record abnormal *Q* or *QS deflections*. These result from the negative potential of the left ventricular cavity being transmitted through the necrotic zone which merely acts as an electric conductor and is incapable of producing any voltage *changes When such an infarct is complicated* by left bundle branch block, the activation of the interventricular septum, which progresses from the right toward the left side, produces initial positivity of the left ventricular cavity, which in turn is transmitted through the necrotic zone of the infarct Thus, the leads obtained *from the epicardial surface directly over* this region will always contain initial R waves regardless of the extent of the infarct During the later part of QRS the secondary R peak fails to develop in leads located directly over the trans-

an S wave

vity, which

ree wall of

fect extends far

corded (V and V)

However, an S wave *may appear in* leads V and V in left bundle-branch block not associated with infarction, so that this sign *is untrustworthy*

When the areas of the QRS complex are *large* (usually the case in this kind of bundle-*branch block*), there are no typical changes in S-T segment or T wave Appearance of a large Q wave in the left precordial leads in left bundle-branch block should suggest the presence of a septal infarct.[41, 50, 90] *Peri*-infarction should be considered when the ECG has a QRS complex over 0.12 sec *resembling left hundle-branch block and a* Q wave in the left precordial leads [16]

1 Anterior wall infarction (Fig. 51) *may be impossible to diagnose electrocardiographi*-cally, and one may have to rely on the clinical course and the serial changes, if any, in the ECG Complicating infarction is suggested by a small notch (rS or QS type of 0 05 sec.

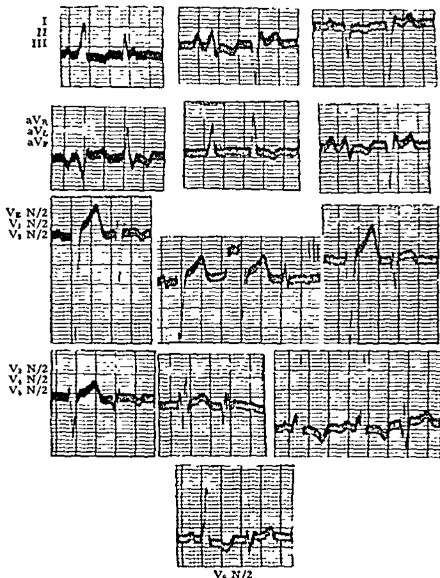


FIG 51 Electrocardiogram from case of anterior myocardial infarction and left bundle branch block, precordial leads recorded at half normal standardization From Wolff [42])

or more) in the terminal part of the QRS complex in the precordial leads, especially V_3 and V_4

2 In posterior wall infarction (Fig 52), concordant T waves may become discordant, but clinical evidence and serial changes in the ECG are necessary to confirm the diagnosis Several cases of left bundle branch block have been described in which electrocardiography showed signs of left bundle-branch block in the limb leads, of right bundle-branch block in the precordial leads, and qR deflections in lead aV_1 [6]- These are instances of myocardial infarction of the septum and of the posterolateral myocardium, and as might be expected, high-grade auriculoventricular block may be found

With intermittent left bundle-branch block, the signs of infarction may be completely suppressed during the block and appear during intervals of normal conduction (Fig 53) Apparently, the conducting pathways are only partially damaged so that normal conduction (and the characteristic signs of infarction)

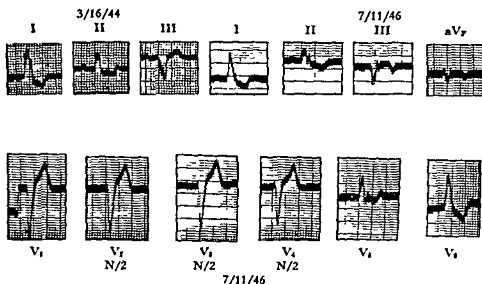


FIG 52 Electrocardiogram from case of posterior myocardial infarction and left bundle branch block, V_2 V_3 and V_4 recorded at half normal standardization (From Wolff)

FIG. 53 Transient left bundle-branch block suppressing signs of anterior myocardial infarction, when conduction was normal (bottom tracing), the T waves were inverted in V_2 to V_5 (From Somerville and Wood)

may appear when the cardiac rate is slowed. This slowing may be induced by ergotamine tartrate intravenously or by pressure on a hyperactive carotid sinus [41]

Rarely, the diagnosis of infarction may be made when premature contractions appear on a tracing dominated by the signs of bundle-branch block; in one case, the diagnosis was made because there was trigeminal rhythm.[9]

WOLFF - PARKINSON - WHITE SYNDROME The syndrome is characterized by a short P–R interval and a prolonged QRS complex When it is associated with a large infarct, the diagnosis is not difficult, but when T wave changes only are found a definite diagnosis can be made only if the conduction can be restored to normal This can be accomplished by quinidine,[84] atropine, amyl nitraite, carotid sinus stimulation, and deep inspiration, separately or in various combinations.[93] Digitalis enhances the anomalous mechanism, it should therefore not be given until a definite diagnosis has been established

SUBENDOCARDIAL INFARCTION[51]

A lesion localized in the subendocardial layer of the heart causes depression of the S–T segment in the overlying leads,[91] inversion of the T wave depends on the extent of the ischemic zone, a Q wave may appear if actual necrosis of tissue has occurred

The "subendocardial" pattern, which typically is depression of the S–T segment, is seen in some patients with angina pectoris during an attack, in "acute coronary insufficiency," and in exercise tolerance or anoxemia tests with positive results The changes in all such cases are transient; they indicate injury to the deepest layer of the myocardium, and if the changes last for more than a day it may be assumed that a histologic change has occurred in this layer The change may consist of isolated subendocardial infarction or it may be a stage in the development of a larger infarct

In a review of the entire subject of subendocardial involvement, Myers and Talmers[51] point out that the contour, as well as the degree, of the S–T depression must be observed In true acute subendocardial injury, a 1 mm or more horizontal or sagging depression of the segment occurs in patients who have not been given cardiac glycosides. In the pseudodepression of "spontaneous" S–T changes, tachycardia is usually present and the T_P wave is exaggerated, the S–T junction drops 0 5 mm or more below the P–R junction, and the S–T segment ascends continuously in a concave arc

ELECTROCARDIOGRAPHIC SIGNS OF CORONARY INSUFFICIENCY AND OF "MINOR INFARCTION"

I have commented at several other places in this book on the frequency with which acute impairment of the coronary circulation (aside from angina pectoris) is found clinically This comprises the group of cases described by Master as "acute coronary insufficiency." When the changes (usually S–T segment changes alone, without Q waves) persist for more than a day, it is probable that there is subendocardial infarction or small mural infarct Papp and Smith[76] describe these as "slight" myocardial infarction I would call these "minor" myocardial infarction, the important point being that when cardiographic or clinical signs persist for more than a few hours, it is highly probable that there is necrosis of heart muscle somewhere in the heart It would seem to me wise to restrict the term "coronary insufficiency" to a reversible and transient process, acknowledging the fact that many cases so described are truly infarctive in nature

Cosby and associates[9] discuss the vectorcardiographic and electrocardiographic attributes of this fairly large group of patients They call attention to the fact that, in contrast to major infarction, about three fourths of the processes are anterior and only about a quarter are posterior Miller, Burchell, and Edwards[50] point to "the greater degree of narrowing of the anterior descending coronary artery" as an explanation for the fact that 76 per cent of their cases involved the anterior wall

An even more puzzling category comprises those patients who show only T wave inversion in the presence of symptoms, such as cardiac pain, of coronary disease There are no QRS complex or S–T segment abnormali-

ties The inversion of T may be transient, it may persist for a long time, perhaps for life Usually when detected clinically, there are no laboratory evidences of myocardial infarction.

In the majority of such instances, the downward T is a relic of infarction in the past, remote or recent When it is transient, it may be regarded as an evidence of "coronary insufficiency"[11] When more persistent and especially if accompanied by clinical symptoms or laboratory evidence (sedimentation rate, etc), there is usually infarction of lesser degree In any case, I agree heartily with Schlant, Levine, and Bailey[7] who feel that isolated inversion of the T waves cannot be dismissed lightly under clinically suspect circumstances Deeply inverted T waves in the precordial leads usually mean subendocardial infarction[8,1]

The important clinical morals to be drawn from this discussion are that (1) transient ST–T changes are found in reversible insufficiency of the coronary circulation, (2) it is wise to insist on QRS abnormalities of a shifting nature before making the diagnosis of acute major myocardial infarction, (3) minor infarction, usually benign and implying a favorable outlook, may be found with only ST–T changes

AURICULAR INFARCTION

The electrocardiographic features of this type of infarct are auricular ectopic rhythms, consisting of auricular extra beats and auricular flutter or fibrillation, and auriculoventricular block of varying degree The tracing often changes from day to day Elevation of P–Ta, or more often, depression, may be present, especially in leads II and III There may be an abnormally short P–R interval, with upright P waves[9]

ANGINA PECTORIS

The ECG in angina pectoris is often abnormal between spasms, since there may be sufficient myocardial fibrosis to affect the tracing A major infarction may have occurred in the past, with residuals which appear in the tracing In a patient with such electrocardiographic changes, cardiac pain, even if slightly atypical, is sufficient ground for assuming that the patient is suffering from true angina pectoris

A "distinctive and mutable" electrocardiographic picture, which Evans[13] describes and considers characteristic of coronary arteriospasm, consists of the following features (1) The T wave is inverted in leads CR_1 to CR_4 and sometimes beyond this to CR_7, the T wave is usually inverted in lead I as well (2) There are no significant Q wave or S–T depressions I have often seen transient T wave changes in patients complaining of precordial pain; cardiac ischemia is probably the cause of these changes, whether or not vasospasm is basically responsible, as Evans suggests

Often however the resting electrocardiogram is entirely normal (in 17 per cent of persons with angina pectoris and no history of previous infarction) Even if the patient's symptoms are quite typical of classical angina pectoris, the physician may wish to have graphic evidence of myocardial involvement If the symptoms are even slightly atypical, the cardiogram will play an indispensable role in *differential diagnosis. Every effort should be* made to obtain transient electrocardiographic changes, and any one of several measures may be used

RECORDING THE ECG DURING AN ATTACK The tracing during an attack may not deviate from the resting state, but occasionally transient changes exactly mimic those of acute infarction—deep Q waves and deeply inverted, coved T waves Somewhat more often, the changes resemble those of subendocardial infarction

A normal ECG obtained during an attack of pain does not rule out the possibility of angina pectoris, some test must then be used which may induce temporary anoxemia, with resulting changes in the ECG A *positive* result of such a test is the finding of the characteristic changes of spontaneous angina and subendocardial ischemia, and, rarely, those of major infarction The technics and electrocardiographic criteria are given here as they are described by the originators of the anoxemia test and of the exercise tolerance

tests. Measurement of the Q–Tc interval probably adds to the accuracy of whatever test is used.[69]

ANOXEMIA TEST The anoxemia technic most often used is that described by Levy [38]

A tank containing a mixture of 10 per cent oxygen and 90 per cent nitrogen furnished an unvarying concentration of oxygen in the inspired air The oxygen mixture was admitted at a rate comparable to that of normal pulmonary ventilation The gas was allowed to flow through a humidifier, into a rubber bag, which was kept full but not distended Two flutter valves were incorporated in such a way that the mixture was inhaled during inspiration and exhaled during expiration without rebreathing A two-way valve at the mouthpiece enabled the observer to connect the patient to the apparatus while he was breathing room air, and thus accurately to record the time at which the subject began breathing the low-oxygen mixture A tank containing 100 per cent oxygen was also in the circuit, so that, if desired, by turning a needle valve, anoxemia could be relieved quickly.

Observations were made at least two hours after the last meal The temperature in the room at which the test was made was kept reasonably constant at about 72° F The subject was allowed to rest quietly in bed from a period of thirty minutes to one hour The procedure was explained and he was told that if he experienced pain in the chest or arms he should at once raise his hand The electrodes were applied and remained in place throughout the test The mouthpiece of the gas apparatus was then inserted and the nose clamp adjusted The subject was allowed to breathe room air through the valve of the apparatus for a few minutes At this time a four-lead electrocardiogram was taken as a control (This control electrocardiogram is always checked before the test is begun) The precordial lead was the one commonly designated IV F The test was then started by closing the valve, the subject was unaware of this maneuver

Stewart and Carr,[72] in a recent comprehensive review, in which they discuss other technics, add

Electrocardiograms are then taken at five-minute intervals through a twenty-minute period, unless substernal or precordial pain or discomfort occurred earlier At the completion of the test the patient inhaled 100 per cent oxygen for a period of one minute, or until pain had disappeared Electrocardiograms were also taken at intervals of one, five, and ten minutes after starting to breathe 100 per cent oxygen In each lead measurements of the deviation of the RS-T junction were taken as the difference between the point just preceding the initial deflection of the QRS and the point immediately following the final deflection The measured complexes should run horizontally, the deflection of the string should be accurately standardized and the skin resistance kept low

The criteria for a test positive result, as given by Levy,[38] are

1 The arithmetical sum of the RS–T deviations in all four leads (I, II, III, and IV F) totals 3 millimeters or more

2. There is partial or complete reversal of the direction of the T wave in Lead I accompanied by an RS–T deviation of 1 mm or more in this lead.

3 There is complete reversal of the direction of T in Lead IV F, regardless of the RS–T deviation

The incidence of positive tests in persons with known coronary disease and angina pectoris is reported variously between 30 and 61 per cent. In a wide and varied collection of anginal patients, using Levy's technic and criteria, the percentage of positive tests is about 50 per cent [52] Results of a follow-up study by Mathers and Levy[46] would seem to indicate that the prognosis for patients with positive test responses is less favorable than for those whose response is negative, and they conclude that the many uncontrollable variables which influence atherosclerosis make accurate predictions about the course of coronary heart disease in any one patient impossible

Negative results do not rule out the possibility of coronary disease, and false positives may occur "Functional" changes are seen occasionally These are discussed on page 166

Reactions to the anoxemia test, few of them serious, are most commonly vasovagal attacks, weakness, sweating, pallor, slowing of heart rate, fall in blood pressure, lightheadedness, and syncope, occasionally there are drowsiness, fatigue, choking sensation, heavy sensation in the chest, tingling and numbness of the fingers, hyperventilation, anxiety, and fear [52] Vasovagal reactions can be expected in about 5 per cent of subjects undergoing the test Myocardial infarction during the test has

been described, and 2 deaths have been reported, both of the patients probably had acute infarction when the test was begun [23]

Anginal pain may occur during the test, whether results are positive or negative, and no apparent correlation has been found between the occurrence of pain and the electrocardiographic changes Except in cases in which payment of insurance is involved, it is probably advisable to consider pain as a sign of true coronary insufficiency.[52]

with electrocardiography seem to have been Scherf and Goldhammer [74] Master[44] made this test popular, and his "two-step" test is now widely used Although any method which will induce the strain of exercise may be used, it is wiser to employ Master's standardized procedure if a cardiac laboratory is not available.

In the single "two-step" test, the patient, with electrodes in place, walks over the two-step stairs (Fig. 54) the number of ascents

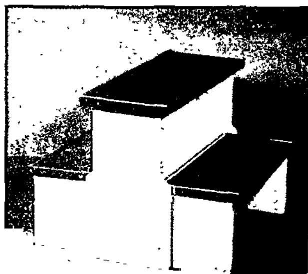


FIG 54 "Steps" for Master two-step exercise (Courtesy of Mr Everett M Hill)

(complete trips over the steps in one direction) as determined from the table based on sex, age, and weight (Table 18) Each step is 9 in high, and the test is to be completed in 1 5 minutes Tracings are recorded immediately, 2 minutes, and 6 minutes after completion of the test, since there may be a latent period before changes appear in the ECG.[21, 73] To avoid dizziness, the patient changes direction after each trip by turning toward the examiner each time If the results of the single test are normal, the double test may be performed at least 1 hour later by patients for whom, in the examiner's opinion, it would be a safe procedure. In this test, twice the number of trips

The contraindications to performing the test are: congenital heart disease, rheumatic valvular disease, pregnancy, myxedema, epilepsy, severe anemia, and marked emphysema or other pulmonary disease A routine 12 lead ECG should be taken before starting the test to rule out the presence of infarction.[58] Any evidence of infarction within the preceding 4 months, or the presence of congestive failure are absolute contraindications

EXERCISE TOLERANCE TESTS Exercise is a simple method of testing a heart suspected of harboring coronary disease. The first to describe an exercise test in combination

TABLE 18 STANDARD NUMBER OF ASCENTS FOR TWO-STEP TEST[43]

Weight, pounds	Age, years												
	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
Males													
40–49	35	36											
50–59	33	35	32										
60–69	31	33	31										
70–79	28	32	30										
80–89	26	30	29	29	29	28	27	27	26	25	25	24	23
90–99	24	29	28	28	28	27	27	26	25	25	24	23	22
100–109	22	27	27	28	28	27	26	25	25	24	23	22	22
110–119	20	26	26	27	27	26	25	25	24	23	23	22	21
120–129	18	24	25	26	27	26	25	24	23	23	22	21	20
130–139	16	23	24	25	26	25	24	23	23	22	21	20	20
140–149		21	23	24	25	24	24	23	22	21	20	20	19
150–159		20	22	24	25	24	23	22	21	20	20	19	18
160–169		18	21	23	24	23	22	22	21	20	19	18	18
170–179			20	22	23	23	22	21	20	19	18	18	17
180–189			19	21	23	22	21	20	19	19	18	17	16
190–199			18	20	22	21	21	20	19	18	17	16	15
200–209				19	21	21	20	19	18	17	16	16	15
210–219				18	21	20	19	18	17	17	16	15	14
220–229				17	20	20	19	18	17	16	15	14	13
Females													
40–49	35	35	33										
50–59	33	33	32										
60–69	31	32	30										
70–79	28	30	29										
80–89	26	28	28	28	28	27	26	24	23	22	21	21	20
90–99	24	27	26	27	26	25	24	23	22	22	21	20	19
100–109	22	25	25	26	26	25	24	23	22	21	20	19	18
110–119	20	23	23	25	25	24	23	22	21	20	19	18	18
120–129	18	22	22	24	24	23	22	21	20	19	19	18	17
130–139	16	20	20	23	23	22	21	20	19	19	18	17	16
140–149		18	19	22	22	21	20	19	19	18	17	16	16
150–159		17	17	21	20	20	19	19	18	17	16	16	15
160–169		15	16	20	19	19	18	18	17	16	16	15	14
170–179		13	14	19	18	18	17	17	16	16	15	14	13
180–189			13	18	17	17	17	16	16	15	14	14	13
190–199			12	17	16	16	16	15	15	14	13	13	12
200–209				16	15	15	15	14	14	13	13	12	11
210–219				15	14	14	14	13	13	13	12	11	11
220–229				14	13	13	13	13	12	12	11	11	10

From Master Am Heart J 10 497, 1935

are taken in 3 minutes In about a third of the patients with abnormal results in the double test, the results of the single test are normal

As given by Klakeg and associates,[50] the test consists of 40 ascents and descents Complaints of fatigue, dyspnea, or chest discomfort are cause for terminating the test In my patients, the test is stopped if the patient complains of chest pain or pressure Some workers do not consider the exact amount of exercise important, and sometimes carry the test to the point of pain or dyspnea[57] A larger percentage of positive test results may be expected if the test is performed until tachycardia supervenes,[98] a cold stimulus may also increase the number of positives In my opinion, these technics are not so safe as the one described by Master

The test is influenced by food, or exercise within 1 hour preceding the test, by nitroglycerin, tobacco, and digitalis The test is probably best done at the time of day when the patient usually suffers attacks of angina pectoris and the value of the results might be enhanced by taking the tracing during the exercise, however this is scarcely feasible except by the use of a treadmill technic[99]

The two step test is most valuable in evaluating the 25 per cent of patients with chest pain in whom no electrocardiographic or other *signs of coronary disease can be found*

The test should be performed only if nothing in the patient's history suggests recent infarction, and the 12 lead resting ECG taken before the test is normal In my patients, I also insist on a normal sedimentation rate Some prefer the usual bipolar limb leads to the precordial derivations,[7] but recent experience has convinced me that V leads taken from the left side of the precordium provide the most useful information The suggestion that the leads be taken in reverse order after exercise (*i e*, V_8, V_7 [if these are used], V_6, V_5, V_4, V_{3}, V_2, V_1, aV_F, aV_L, aV_R, and then the limb leads) is a good one The most sensitive leads are V_4 and V_5

At the Mayo Clinic,[50] no subject is given the test if it is more strenuous than his usual daily activities or if his exercise tolerance decreased progressively in the period just preceding the test. The test is not given to any patient in whom anginal pain had developed in the preceding weeks, presumably, this is a recognition of the fact that the first appearance of angina may coincide with sudden occlusion of a coronary vessel

The criteria for positive test results are:

1. The RS–T segment depressed more than 2 mm below the isoelectric line, a 1 to 2 mm depression is considered equivocally positive

2 Complete or partial inversion of the T wave, except in lead III S–T depression is more significant than T wave changes[65]

3 Transient arrhythmias, conduction defects, or large Q waves.

The occurrence of anginal pain may be considered evidence of coronary insufficiency except in subjects making claims for indemnification There is little correlation between the appearance of pain and the incidence of positive results, although one report states that positive results are found twice as often among patients in whom pain develops during the test as among those in whom it does not[57]

A positive test result, it is generally agreed, may be regarded as evidence of coronary insufficiency at the time the test was done Such patients probably have coronary artery disease A 5 year follow-up study of 100 patients with positive results revealed that only 29 showed no evidence of coronary disease, of 150 patients with negative results in the single and double test, only 1 had a *coronary occlusion*[48]

Contraindications to the exercise test are the same as for the anoxemia test In addition, the test should not be performed in patients with heart failure or cardiac enlargement

Untoward reactions to the test are uncommon, but at least 5 deaths have been reported[52] Myocardial infarction occurred in 1 patient after exercise, a control ECG had been equivocal, but he had had cardiac pain a few hours before[6] Pain which may persist for a short time after the test is usually abolished by rest, the patient should not be allowed to walk or exercise until the pain has *completely disappeared.*

Negative results of the coronary insufficiency, anoxemia, exercise tolerance, or other tests do not rule out the possibility of coronary disease False positive results may occur in the two-step exercise tests, as in 2 cases of right bundle-branch block with the Wolff-Parkinson-White syndrome[15] "Functional"

changes have been reported in neurotic patients taking the anoxemia or the exercise tolerance tests.[5, 60] Use of ergotamine tartrate before the test, or preferably dihydroergocornine, reportedly "normalizes" the tests in neurotic individuals, but not in patients with coronary disease [4, 47] On the other hand, the differential diagnostic value of this alkaloid has been denied

In some cases of coronary disease, an abnormal electrocardiographic pattern reverts to normal after the exercise tolerance test.[29] According to some observers, the appearance of frequent premature beats during the test is probable evidence of disease,[24] while others insist that additional positive features must be present for a diagnosis of coronary disease [51] The exercise tolerance test had been reported to be useful in evaluating bundle-branch block, with positive results in 50 per cent of the cases of coronary heart disease associated with such block [15] In severe left bundle-branch block, I have not found the test useful

COMPARISON OF EXERCISE TOLERANCE AND ANOXEMIA TESTS

Exercise tolerance test	*Anoxemia test*
No special apparatus required	Special apparatus needed
Produces type of strain which usually causes angina	Patient recumbent and resting
Pain may last after discontinuance of test	Oxygen available if necessary
May be delay in recording tracing after exercise	
Movement and tachycardia may distort the ECG	

With either test, a positive result is much more significant in the differential diagnosis than a negative one

The results of the two tests are not closely correlated, one may be positive when the other is negative. A comparison of the results of the two tests in 23 patients showed that in 12 patients the results were negative in both tests, positive in both in 5 patients, and in 6 patients thought to have heart disease the result was positive only in the exercise test [63]

A well-documented evaluation of the stress tests has recently been reported.[65] The double two-step test was performed in 827 patients, most of them between the ages of 45 and 54, 301 of this series also took the anoxemia test, the average follow-up period was 6 years.

Among the 219 patients with abnormal ECGs in the two-step test, 48 died and 16 suffered acute infarctions with recovery, 133 of this group showed S–T depression, and of this group 42 died and 12 had infarctions, of the 86 who showed T wave or conduction changes 6 died and 4 had infarctions Depression of the S–T segment would therefore seem to be the more meaningful sign Of the 608 patients in whom test results were normal, 45 died and 15 had infarctions Of 12 patients in whom both tests gave positive results, 5 died and 6 had progressive coronary disease Of 182 patients with negative results in both tests, 10 died and 123 were normal after 7 years Of the 104 patients with negative anoxemia results but positive exercise responses, 24 died and 14 had infarctions In only 2 patients were the results of the anoxemia test positive and of the exercise test negative I prefer the exercise test and use it exclusively when an office test is necessary.

OTHER TESTS *1* The "meal test"[54] is based on the fact that an ECG taken after the ingestion of food is more likely to show abnormalities [66] The test is a simple one to use in office practice In doubtful cases, I usually ask the patient to come back again after a heavy meal The electrocardiographic changes should be clear cut; some changes, such as an increase in heart rate and decreased size of the T waves, may appear in normal persons

The exercise test may be combined with the meal test [30] In most cases, there are no advantages over the two-step test alone, but in an occasional young patient with equivocal angina pectoris in whom the results of the exercise test are negative, the combined tests may be revealing Persons with atypical distress after meals also seem to be logical candidates for the combined tests. Although in rare cases previously negative test results become positive, routine use of the combination does not seem justified

2 The ergonovine test consists of the

intravenous administration of ergonovine maleate. This, it has been reported, produces the clinical and electrocardiographic pictures of coronary insufficiency, it is said to be safe and more sensitive than either the anoxemia or the exercise tolerance test.[61] A recent report confirms the results of the ergonovine stress test, both in animals[63] and in man [64]

3. Epinephrine has been similarly employed,[30, 87] but there have been no reports on its use in recent years

4. Intravenous administration of pitressin has been proposed as a test [5, 73] But since it is a potent vasoconstrictor, its use for test purposes would seem to be at least potentially dangerous

5 Intravenous administration of salt has also been proposed as a substitute for other tests [35] Hypertonic salt solutions, intravenously, did not produce significant electrocardiographic changes,[1] since the test is also potentially dangerous, I would not advise its use.

6 The use of cigaret smoking as a test is discussed in Chapter 5

CHRONIC CORONARY DISEASE

Several categories of ECG may be found in chronic coronary disease the tracing may be normal, it may be normal despite positive results in the exercise tolerance or anoxemia tests, it may show signs of old infarction, or various nonspecific changes may be present The electrocardiographic residuals of old infarction may be absent, minimal, moderate, or quite unmistakable

If the infarction was in the anterior wall, the T waves may be low, isoelectric, or inverted in leads I and II, and in the precordial leads in any combination, lead II being the least often involved. Small Q waves may remain, or be represented by an R wave of diminished amplitude. If the infarction was in the posterior wall, the T wave may be inverted in lead III, and a Q wave often remains

Similar changes may be found in patients without a history of acute infarction; when they are definite, the patient has had an infarction with such slight symptoms as to be overlooked or there have been gradual infarctive changes over a prolonged period Barring evidence to the contrary, such changes should be accepted as signs of coronary disease

Bundle-branch block is most commonl caused by coronary atheromatosis. This bloc may be found in any type of heart diseas and, very exceptionally, in presumably norm. hearts. Every case of bundle-branch bloc should be considered as a case of coronar disease in the absence of evidence to th contrary.

Auriculoventricular block, with its pro longed P–R interval, may be the first sign c coronary disease. It may also be found i many other conditions More severe block common in coronary disease, and a complet heart block which occurs for the first tim in a person over the age of 40 should b held as evidence of coronary sclerosis an a myocardial lesion

Extrasystoles, when due to coronary dis ease, are usually associated with other ab normalities Occasionally, they may be foun as the first sign of coronary disease. Mai complexes of unusual width (over 0 16 sec in ventricular premature contractions are sai to occur more often in persons with hear disease than in normal individuals; inversio of the T wave in the beat following a ver tricular extra beat, may be taken as evidenc of coronary insufficiency.[36]

A prolonged Q–T interval may be foun in coronary disease, but is more apt to occu in acute infarction and in disturbed electro lyte metabolism

The S–T segment may be depressed in chronic coronary disease, and is depressed in ischemia of the subendocardial layer of th myocardium (angina pectoris, subendocardia ischemia or infarction) Three varieties o depression have been described [11] earl (sickle or claw) depression, middle (trough depression, and late (plane or wing) depres sion, considerable significance is attached t the plane or wing depression, especially if i occurs in lead IIIR It is my opinion, too that such S–T segment depressions shoul be regarded as a probable result of coronar disease, provided other disease is absent.

The U wave, if present, is normally upright It may be inverted in hypertension or in coronary heart disease without other change being present.[14, 32, 34, 77] The inversion is mos often seen in leads I or II or in precordia lead 4 U wave inversion may also occur a part of a positive reaction to the exercis

test,[26, 57] in which case it may be associated in the precordial leads with a sharply pointed, symmetric T wave[57] The U wave is said to be often inverted in leads III and V_R in the normal ECG.[22] In any case, the U wave gives no information which is not obtainable by study of the T waves.

The P wave may be distorted as a residual of an old auricular infarct I have never found P wave changes in coronary disease which were not associated with other abnormalities.

Slurring or notching of the QRS (main) complex, not present on earlier ECGs must be considered as evidence of myocardial damage, in older persons presumably due to coronary disease. Minor slurring, especially in lead III, is not incontrovertible evidence of coronary disease except when it represents a change from a previous tracing Notching of the QRS complex in precordial leads 4, 5, and 6, when these show a qR pattern, should be regarded as evidence of coronary involvement.[14]

T wave inversion or depression is often a residual sign of old infarction Many conditions induce T wave changes, but in their absence low or inverted T waves, except in lead III, should cause a search for other evidence of coronary disease A low T wave in lead I (lower than T_2) should be regarded with suspicion, I have found it to be an important sign of early coronary disease.

Electrocardiographic changes in other conditions may be confusing They are discussed in Chapter 13

NORMAL ECG IN CORONARY DISEASE

Although the value of the ECG in the diagnosis of coronary disease is often depreciated, the foregoing discussion has perhaps refuted this point of view.

In chronic coronary disease, the resting ECG is often within normal limits Changes will appear only if the myocardium, not the vessel wall, is injured However, an ECG taken during an attack of anginal pain or during a test which produces cardiac ischemia will often show abnormalities.

In major coronary occlusion, *i e*, myocardial infarction after occlusion of a major blood vessel, correct electrocardiographic survey, with repeated observations, almost invariably discloses changes in the ECG. I have not seen even one case of infarction severe enough to cause shock or signs of tissue necrosis (fever, leukocytosis, etc.) in which the ECG has remained normal throughout the course of the illness However, it is true that even in fatal cases the tracings may occasionally be atypical and not conform to the classic electrocardiographic pattern, but seldom are they "normal" In practice, if rest is enforced as soon as there is enough clinical evidence to suspect early infarction, serial tracings on the following days will provide the opportunity for confirming or disproving the diagnosis

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CHAPTER 11

Case Reports

THE CASE histories in this chapter illustrate many of the points made earlier in the book, especially in Chapter 10

CASE 1. IATROGENIC HEART DISEASE

The patient, a 43 year old man with normal blood pressure, stockbroker by profession, had 3 years before sensibly decided to have a thorough medical examination on reaching his fortieth birthday On the basis of the ECG taken at that time (Fig 55*A*), he was told that he had serious organic heart disease, presumably coronary occlusion with myo cardial infarction

The effect on the patient was profoundly disturbing He immediately resigned from an athletic club, sold part of his business, gave up golf, refrained from sexual relations, and, generally speaking, withdrew from his former active participation in life He became morose and refused to seek further medical advice, fearing that he would be told to curtail his activities still further.

After 3 years, he sought psychotherapy at his wife's urging The psychiatrist referred him to a cardiologist, who was unable to find any evidence of cardiac disease From the ECG (Fig. 55*B*), it was apparent that in the earlier one the right and left arm electrodes had been transposed, for the earlier tracing was reproduced exactly when this transposition was made. The patient, though assured that he did not have heart disease, still needed several months of intensive psychotherapy before a complete cure was obtained

The technical error of lead transposition resulted in a mistaken diagnosis of organic heart disease and caused a severe case of iatrogenic heart disease

CASE 2. INFARCTION IN 32 YEAR OLD MAN

The patient, an engineer, was seen at the age of 34 He gave a history of myocardial infarction 2 years earlier and angina pectoris of increasing severity since then, requiring at the time the ECG was taken (Fig 56) 20 to 30 nitroglycerin tablets daily. The patient's blood pressure was low before, during, and after the infarction His blood cholesterol was 480 mg per 100 cc., 2 older siblings had blood cholesterol values of 410 and 425 mg, respectively, his mother, who had had a myocardial infarction at the age of 55, had a blood cholesterol value of 510 mg.

The angina became so severe that the surgical relief of poudrage (pericardial instillation of talc) was required The patient now feels much better, and uses only 5 tablets of nitroglycerin a day There have been no signs of cardiac decompensation The electrocardiographic changes, which show extensive an-*terior wall involvement, have not been affected by the operation*

The features of this case are the youth of the patient, the family history of hypercholesterolemia, and the partial relief of severe angina pectoris by surgical means

CASE 3 AURICULAR AND VENTRICULAR INFARCTION IN 39 YEAR OLD WOMAN

At the age of 37 the patient had had an anteroseptal infarct, 2 years later she had an acute posterior wall infarction The ECG (Fig 57) showed interesting P wave changes in all the precordial leads The limb leads are not reproduced The patient died on the fourth day of illness Postmortem examination showed. (*1*) old anterior infarction; (*2*)

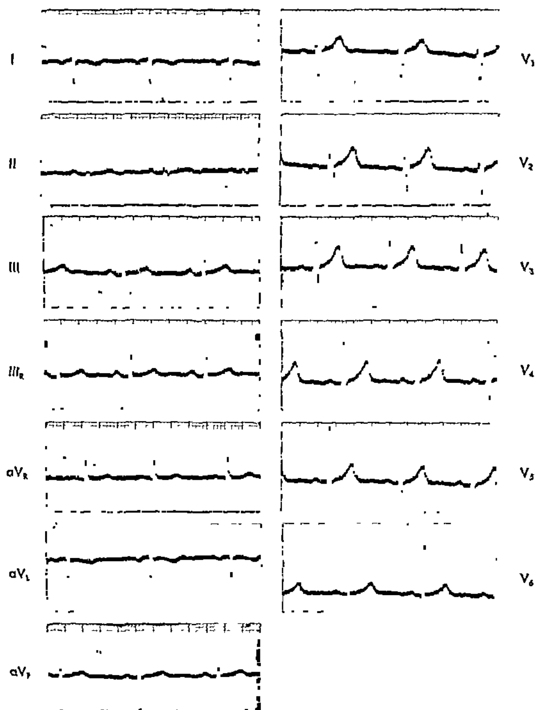


FIG 55A

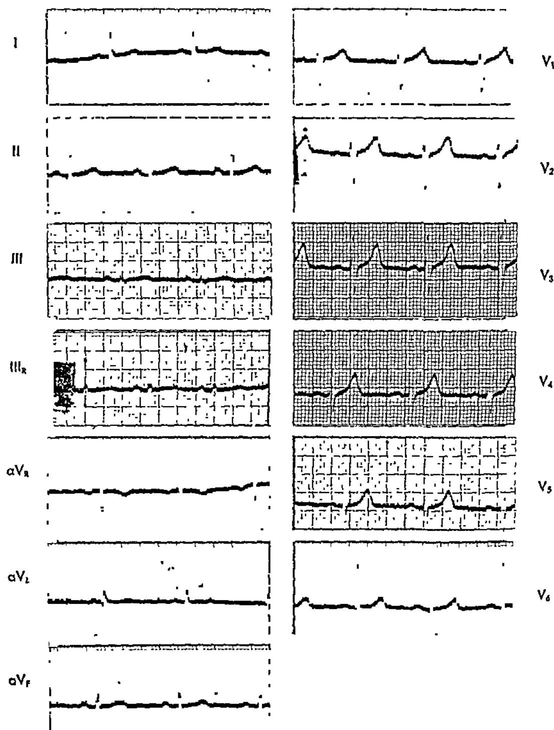


FIG 55B

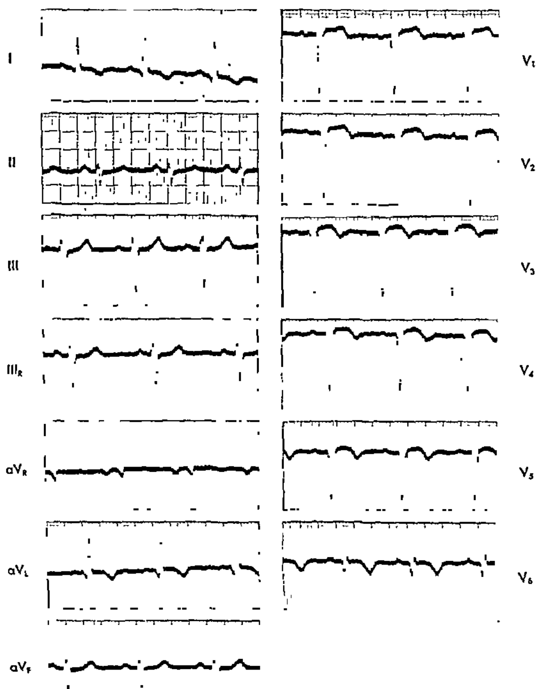


FIG 56

fresh posterior wall infarction, (3) a circular area, 2 5 cm in diameter, of infarction in the left auricle.

This case is a rare example of auricular infarction *Myocardial infarction is uncommon in* a woman under the age of 40, but the patient was a diabetic.

CASE 4. SUPERIMPOSITION OF INFARCTIONS

The patient is a 58 year old tobacconist. At the age of 54 he had had an acute posterior wall infarction; his blood pressure at that time was normal, a mild angina pectoris had been present for a year before the infarction The only unusual features of his first infarction were a rise in temperature to 103 6° F. for 2 days, and a leukocyte count of 34,000

After discharge from the hospital, he was able to resume his usual work, attacks of angina were rare and were completely relieved by pentaerythrityl tetranitrate The ECG shown here (Fig 58) was taken 3 days after a second infarction, clinically less severe than the previous one The patient is now suffering from increasing dyspnea and more frequent attacks of angina pectoris The ECG, which has remained constant, shows easily identifiable anterior and posterior wall changes

As may be seen from this case, high fever and marked leukocytosis are compatible with a mild clinical course of myocardial infarction The electrocardiographic changes show fresh anterior wall infarction superimposed on old posterior wall infarction

CASE 5. ANGINA PECTORIS ADVERSELY AFFECTED BY SMOKING AND BY MEALS; MINOR MYOCARDIAL INFARCTION

The patient is a 56 year old tailor At the age of 49 he suffered an 8 hour attack of precordial pain The ECG taken the following day was interpreted as normal Shortly thereafter he began to complain of angina, which has been gradually increasing in severity Walking to work after breakfast invariably made the pain worse Nitroglycerin relieves his pain quickly, when taken before an exertion expected to produce pain, it prevents the anginal pain. Smoking induces angina invariably; during a month in which he gave up smoking he had almost no cardiac pain

The patient's physical examination was

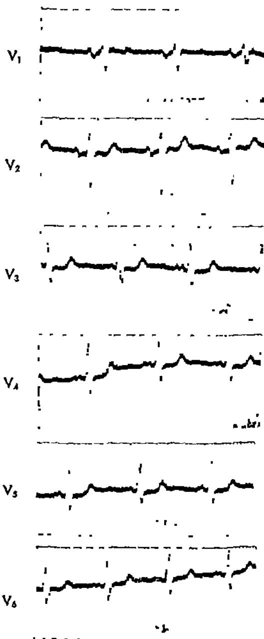


FIG 57

entirely normal His blood pressure has always been about 120 75, his blood cholesterol is normal (212 mg per 100 cc)

A year ago, when he was 55, he consulted an internist who took an ECG (Fig 59 *A*). Immediately thereafter, a Master two-step test gave an intense, positive reaction (Fig 59 *B*). An ECG taken during a spontaneous attack of angina was identical with the one after the two-step test

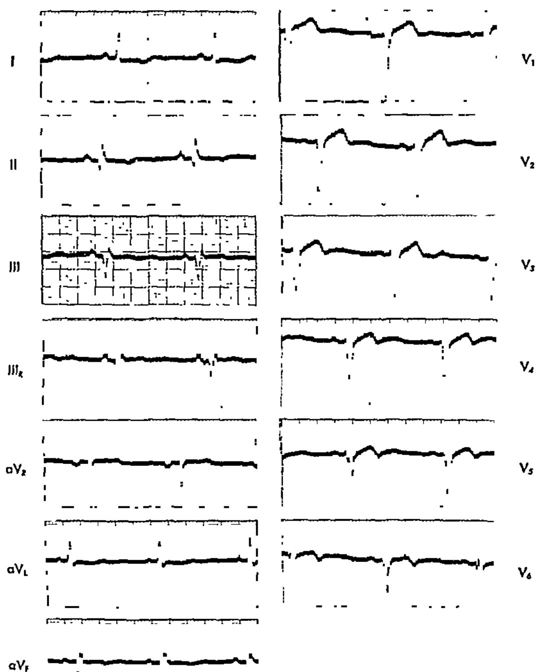


FIG 58

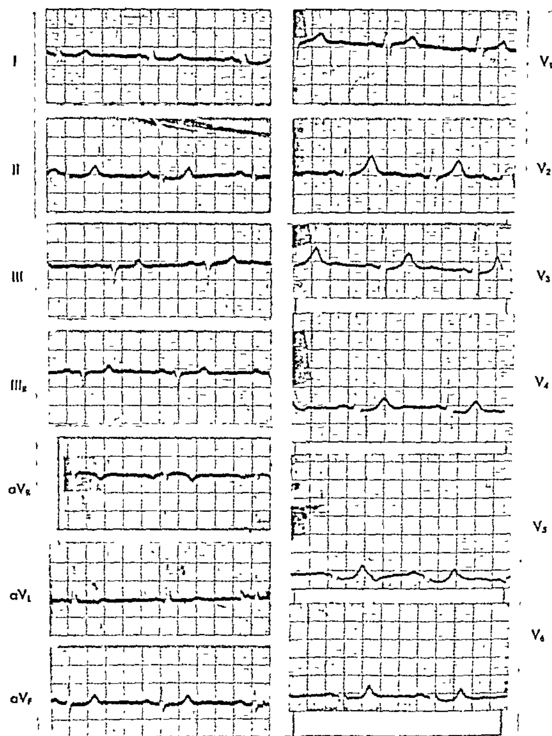


FIG 59A

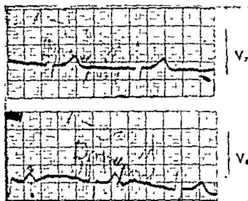


FIG 59A (contd)

While on a visit to another city 5 months later, he suffered an attack of nausea with severe precordial oppression, and an ECG was taken that day (Fig. 59 *C*). On returning to New York 5 days later, another ECG was taken (Fig 59 *D*). He had had no manifestations of shock, or any drop in blood pressure. His sedimentation rate was 25 mm. in 1 hour, his leukocyte count 11,000 at the time tracing *D* was recorded, after 2 weeks, the sedimentation rate subsided to 7 mm., and the white blood count to 6,000 The inverted T waves gradually resumed their normal position

Despite the fact that the ECG did not show the serial changes (Q waves and S–T segment elevation) of a major infarction, it is almost certain that there was necrosis of tissue in the anterior cardiac wall The changes in the sedimentation rate and leukocyte count support this opinion.

This case presents several features worth comment: (*1*) Postprandial exercise is a frequent cause of angina, and breakfast is the meal most likely to be involved (*2*) The exercise tolerance test was positive (*3*) Small areas of infarction have been demonstrated at autopsy in cases showing the same sequence of electrocardiographic changes as in this case, which consisted mainly

I
II
III
V1
V2
V3
V4
V5

FIG 59B

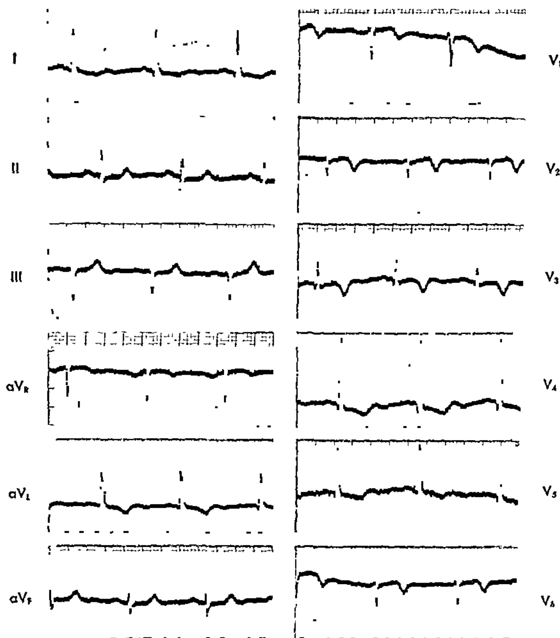


FIG 59C

of T wave changes It is manifestly insufficient to say that the patient described here had only an ischemic area (*4*) This case falls into the category about which there is *considerable dispute* regarding the use of anticoagulant therapy. In the light of present knowledge, I would have given him an anticoagulant at the time when tracing *D* was recorded He might also be a suitable candidate for long-term anticoagulant therapy. Many others, however, would not subscribe to this view

CASE 6 IATROGENIC HEART DISEASE

The patient is a 40 year old architect An ECG was taken when he was 34 because his blood pressure was found to be 160/90. The tracing was identical with that of Figure 60 *A*, obtained 6 years later All the leads up to V_4 were normal and are not reproduced The patient was told that he had coronary heart disease because the main complexes in leads V_4, V_5, and V_6 were deformed, with an

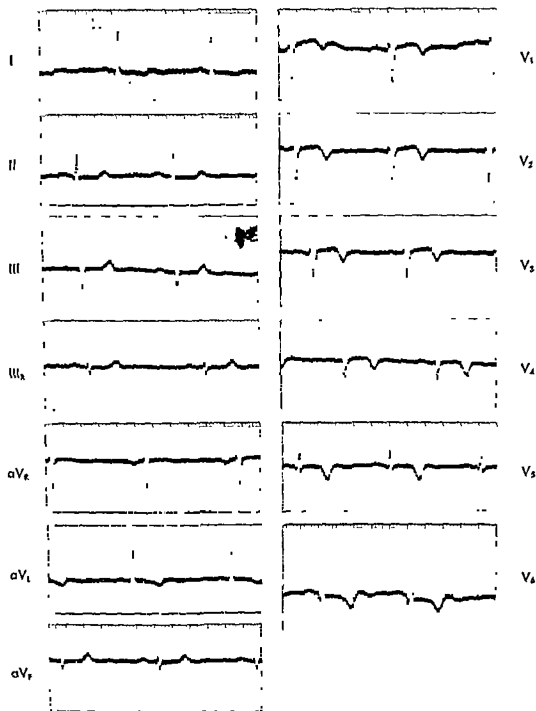


FIG 59D.

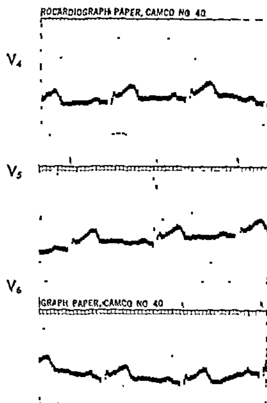


FIG 60A

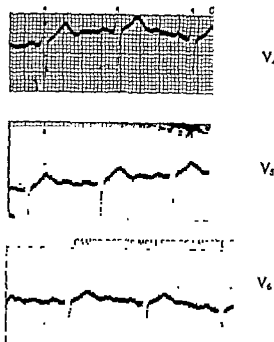


FIG 60B

elevation of the S–T segment The man thereupon gave up all outdoor exercise, and broke off his engagement so that he would not "saddle a wife with the burden of caring for an invalid."

In the following 6 years of inactivity, he gained 42 pounds in weight and had dyspnea on exertion This served to confirm the diagnosis of advanced coronary disease, both to the patient and to his physician At no time did he suffer chest pain, and after the first examination the blood pressure was normal at all times.

The patient reported for a cardiac survey during the absence of his physician on vacation. He came armed with 92 ECGs taken since the onset of his "illness" His blood pressure was 128/72, and his pulse regular at a rate of 72. The heart was normal in size. The blood lipids were normal The only abnormality in the ECG was in the left precordial leads The main complex showed a tiny Q wave, a high R wave with some slurring of the descending limb, and a slightly elevated S–T segment. An ECG taken after a double two-step test showed complete reversion to normal (Fig. 60 *B*). The patient finally accepted the fact that his heart was normal and resumed normal physical activity. His breathlessness disappeared when he lost 30 pounds in weight

Noteworthy conclusions to be drawn from this case are. (*1*) Persistent deviation of the S–T segment unaccompanied by the picture of old infarction does not necessarily indicate heart disease (*2*) A single reading of the blood pressure at a first examination cannot be used as the basis for a diagnosis of "hypertension" (*3*) The breathlessness in this case of iatrogenic heart disease, attributed to cardiac decompensation, should properly have been attributed to obesity and inactivity.

CASE 7. SYNCOPAL ONSET OF ACUTE INFARCTION, WITH POSTERIOR WALL DAMAGE

The patient is a 52 year old architect with normal blood pressure. At the age of 47 he had suffered an extremely severe posterior wall myocardial infarction His story, con-

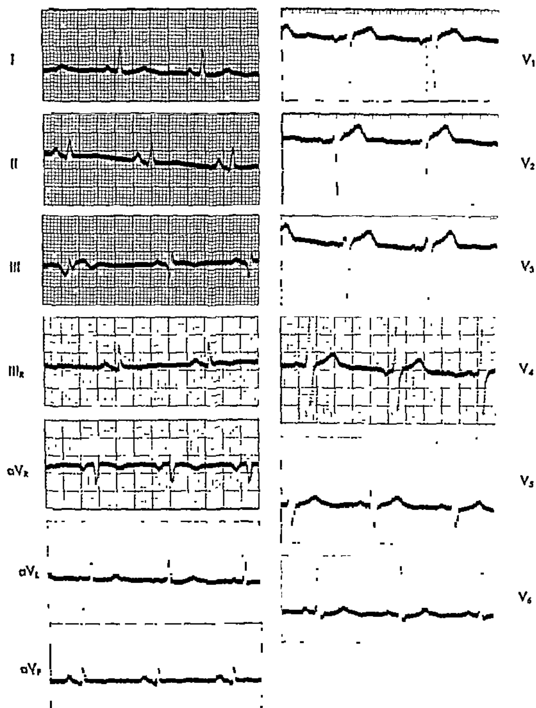


FIG 61

rmed by the hospital record, was of sudden nset of chest pain and syncope, and shock sting for several hours Eventually he made good functional recovery and was completely habilitated economically, cardiac symptoms ere completely absent.

Close questioning brought to light the fact at the onset of his illness was not "the bolt om the blue" originally described by the atient. For about a year before, he had felt

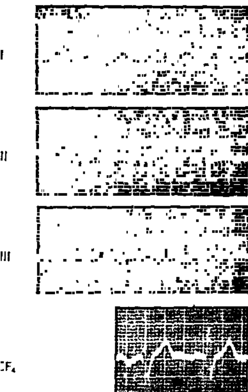


FIG 62A

puffy" on exertion, although his weight had ot increased He had always been of spare ody build For about 6 months he had oticed "turning over of the heart" on exer-on; undoubtedly, he was describing prema-ure contractions During the week before the nfarction, he had suffered from burning ensations in the left arm, with tingling in the eft little finger.

Even without knowledge of the history, old osterior wall infarction could have been uspected from the ECG (Fig 61). The T_{II} vave is low, there is a deep Q wave in lead III and an inverted T wave; in lead aV_F the Q wave is shallow but broad and the T wave is down. Lead IIIR is of small value in this tracing. If anything, lead III becomes more normal in appearance when the patient takes a deep breath Vectorcardiography gave clear-cut evidence of a posterior wall lesion

The noteworthy features of this case are (*1*) The syncopal onset of the infarction (*2*) The extrasystoles on exertion only, this is often noted in coronary disease (*3*) The story of "bolt from the blue" infarction, this is very uncommon, and close questioning, as in this case, may reveal antecedent symptoms (*4*) Although the ECG shows the features of old posterior wall infarction, lead IIIR is uninformative, this is unlike the findings in most other cases of posterior wall lesions

CASE 8. CHANGE IN ANGINAL PAIN INDICATING MYOCARDIAL INFARCTION

The patient is a 60 year old foundry worker with normal blood pressure For about 3 months, the patient had experienced mild substernal pain radiating to the left shoulder, which was easily relieved by rest or a tablet of nitroglycerin, he needed about 3 tablets a week. One day he noted that the pain was spreading to the left side of the jaw and was slightly more severe than usual Several tablets of nitroglycerin gave only moderate relief, and the patient went to the doctor's office instead of to work The pain decreased and after the ECG (Fig 62 *A*) was taken (the first ever obtained) the patient was permitted to go to work, since the tracing was read as normal

For several hours that day the patient lifted and stacked heavy metal parts weighing 30 to 50 pounds each. He refused his dinner that evening, later, the pain returned in somewhat severer form and he vomited A second ECG was taken 14 hours after the first (Fig 62 *B*), this tracing was interpreted as showing an early posterior wall infarction, and the patient was put to bed During the night, the pain became so severe that several injections of morphine were needed. The patient sweated profusely, and his blood pressure dropped from 140/90 to a low of 100/60

The next day oxygen was administered and the pain disappeared, his temperature, however, rose to 102° F and remained at that figure for 2 days. A loud friction rub was

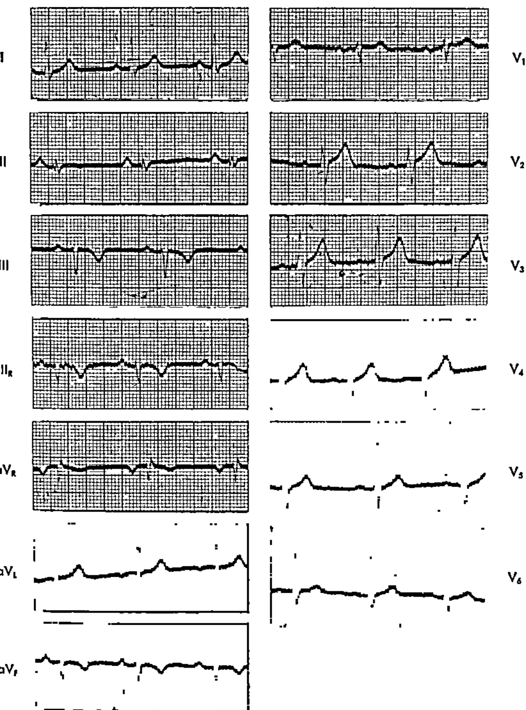


FIG 62B

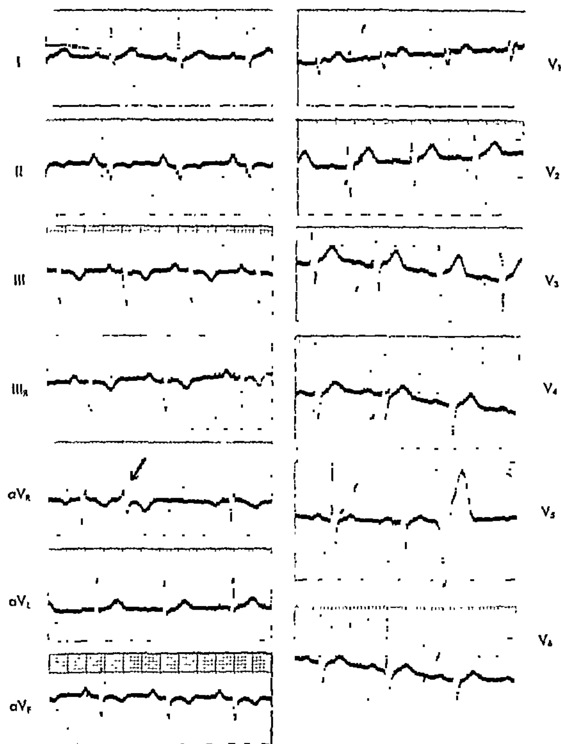


FIG 62C.

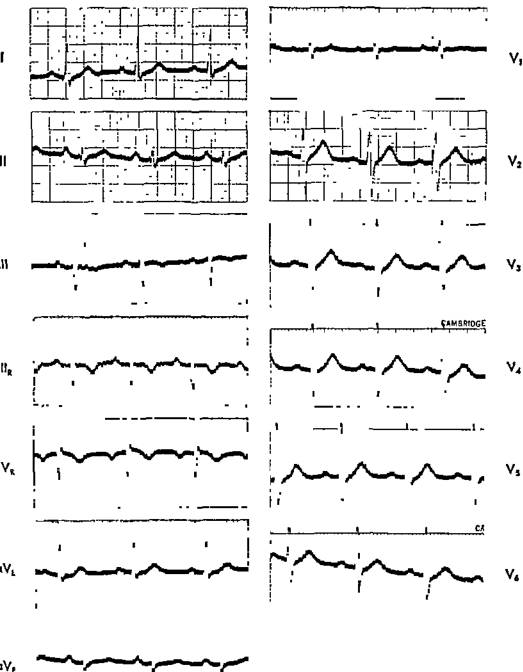


FIG 62D

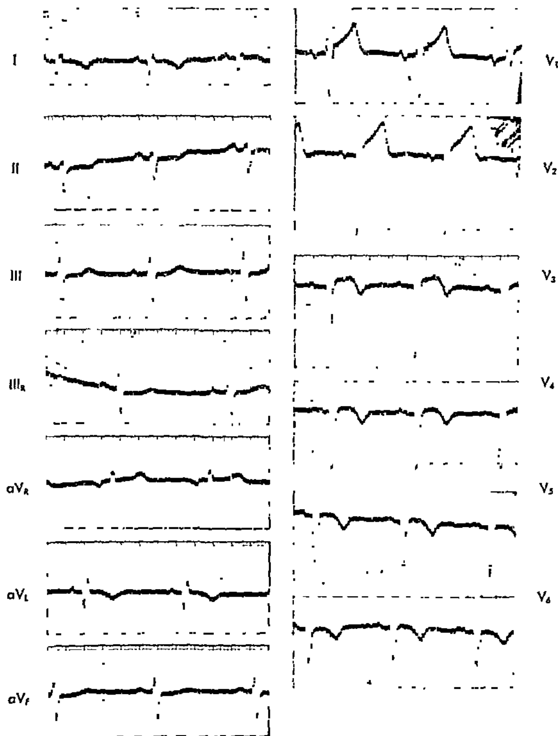


FIG 63

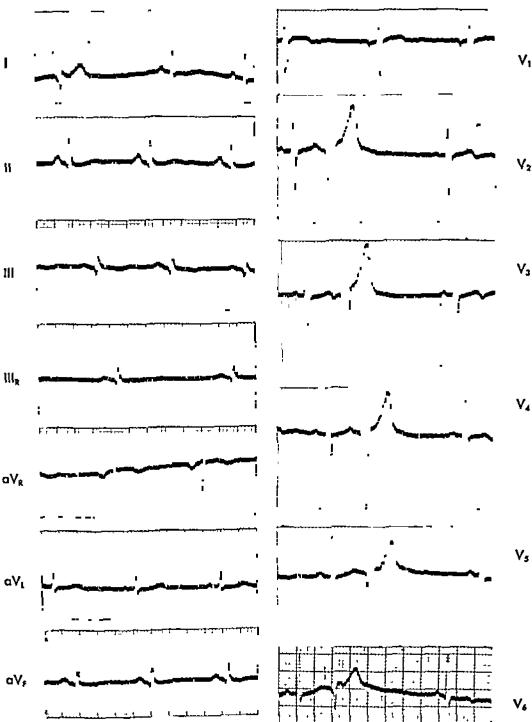


FIG. 64

heard on the second day, the leukocyte count was 16,000, and the sedimentation rate 45 mm. in 1 hour. A third ECG (Fig 62 C) was taken 24 hours after the first For the next 3 days there were no further electrocardiographic changes Several premature ventricular contractions occurred

The patient made a good recovery, 1 year later he had no symptoms and was told by a local physician who took an ECG that he "could never have had a heart attack" Another ECG (Fig 62 D) taken the same day, looked fairly normal, but lead IIIR showed diminution of a small R wave previously present, and a considerable deepening of the T wave

The interesting features of this case are (1) The difficulty of dating the infarction from the appearance of the ECG (2) Although tracings were taken frequently, no changes in the S–T segment were seen (3) The abrupt change in the radiation and in the response to medication of the anginal pain should have been regarded as an indication of an early infarction or of a premonitory phase, the patient should have been put to bed despite the normal appearance of the ECG (4) The appearance of lead IIIR gave positive evidence of old infarction (5) The premature contractions which the patient felt are known to occur in acute infarction, particularly of the posterior wall (6) Oxygen relieved the infarctive pain, as it often does

CASE 9. ANGINA PECTORIS, MAJOR ANTERIOR WALL INFARCTION

The patient is a 59 year old ship's chandler. Angina pectoris was first noted 9 years previously The pattern was quite definite squeezing pain in the substernal area, radiating to the left shoulder joint, on walking 1 block or on climbing less than a flight of stairs, the pain was easily relieved by 1 200 grain of nitroglycerin Cold weather or eating brought the pain on more quickly His blood pressure was 120/175, the ECG was reported to have been normal.

One cold winter morning 6 years ago, at age 53, the angina became more widespread than usual and for the first time extended into the left fingertips Several nitroglycerin tablets were needed to relieve the pain He went to work and carried on his usual activities, but needed 30 tablets of nitroglycerin instead of his usual 5 or 6 a day That night he had some insomnia because of nausea, but went to work the next morning despite increasing angina At 2 p m, the pain became intense and was not relieved by 30 tablets of nitroglycerin within 20 minutes; the patient went into mild shock. The ECG (Fig. 63) showed a major anterior wall infarction. After a stormy 8 weeks in the hospital, the patient recovered and is now back at his customary work He needs an average of 5 to 7 nitroglycerin tablets a week; there have been no signs of heart failure

Since the second week in the hospital, the ECG has shown no change. Old anterior wall infarction is definitely indicated by the changes in leads I, II, aV_L, and the precordial leads.

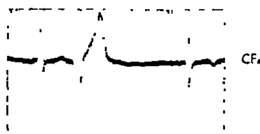


FIG 64 (Contd)

In this case, there was persistence of the Q and T wave changes indicating old anterior wall infarction, a change in the distribution of the anginal pain and in the dosage of nitroglycerin needed to relieve the pain, and alleviation of angina after the major infarction

Any change in the distribution, onset, or relief of anginal pain should lead to immediate investigation The patient should be put to bed at once, on the assumption that infarction has occurred or is impending

Alleviation of angina after major infarction is common

CASE 10 "POST-EXTRASYSTOLIC T WAVE INVERSION" WITHOUT OTHER EVIDENCE OF CORONARY HEART DISEASE

The patient, a 59 year old insurance executive, sought medical advice for "thumps" in his chest which he had felt for several years. His blood pressure was 134/80; the size of the heart was within normal limits; no abnormalities were found in the heart or elsewhere in the body, except for a duodenal ulcer which the patient was known to have had for many years.

The ECG (Fig. 64) shows many premature

ventricular contractions. Of special importance is the "post-extrasystolic inversion of the T wave." In the precordial leads, the T wave in the beat immediately following the extra contraction is inverted instead of being upright, as usual. As yet, the significance of this is not quite clear. Further investigation and a 3 year follow-up have revealed no evidence of myocardial disease in this patient

The phenomenon has been described* as evidence of coronary insufficiency, and I have seen it in 2 cases of angina pectoris

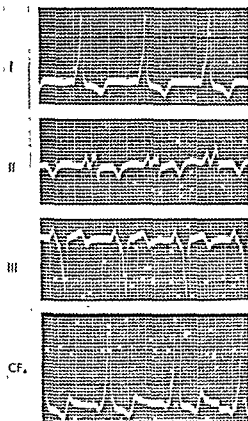


FIG 65A

CASE 11. WOLFF-PARKINSON-WHITE SYNDROME WITH CORONARY DISEASE

The patient was first seen in 1943, when he was 33 years old while on furlough from the Army His blood pressure was normal, he was obese, and he complained about palpitations He had had bouts of palpitations for about 10 years which, however, had never interfered with his work and were not brought on by exertion The ECG taken 3 years later (Fig 65 *A*) shows the presence of the Wolff-Parkinson-White syndrome, the P–R interval is very short, a tiny P wave in lead I is followed almost immediately by the upswing of the R wave, and the main (QRS) complexes are wide and deformed Pressure on the carotid sinus, and administration of quinidine, amyl nitrate, and atropine all failed to restore the heart rhythm to normal

Mild angina pectoris set in 1 year later, and about 3 months thereafter the patient suffered an attack interpreted by Army doctors as a mild myocardial infarction The clinical course was quite definite, including leukocytosis and other features, but the ECG remained unaltered throughout the course

The patient continues to have low-grade angina, but no change has been noted in any of the many ECGs taken, all being identical with the one taken in 1955 (Fig 65 *B*) Vigorous exercise produces cardiac pain, but no changes in the tracing

This case illustrates two points (*1*) The Wolff-Parkinson-White syndrome (short P–R interval, wide QRS complex) may be accompanied by coronary disease (*2*) Electrocardiographic changes are best recognized if the heart rhythm can be restored to normal, for otherwise, as in this case, the changes of coronary disease may not be identified

CASE 12 SUDDEN ONSET OF ANGINA PECTORIS

The patient, a squat, obese, 39 year old clerk, had been in excellent health until 3 weeks before the ECG shown in Figure 66 was taken In the course of the 3 weeks he had begun to suffer from gradually increasing angina pectoris of the classic variety The patient emphasized the abrupt onset of his symptoms "One day I was perfectly well, the next, it hurt me in my chest and arm when I walked or played poker "

Neither the history nor the laboratory evidence when the patient was first examined suggested an acute myocardial infarction The ECG, however, showed clear-cut evidence of posterior wall infarction Just when the acute episode occurred cannot be determined, but it seems reasonable to suspect that it was in close connection with the onset of the angina

* *See* reference 36, Chapter 10

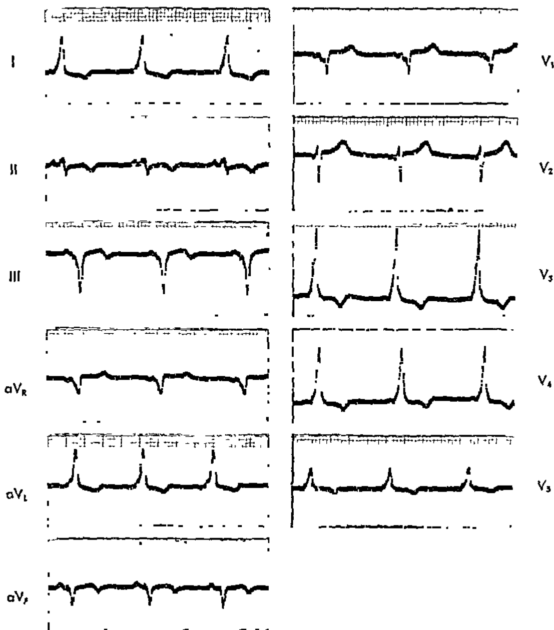


FIG 65B

There were no further changes in the ECG pattern, an indication that the infarction was at least several days old, and probably much older. An acute major infarction occurred 2 years later.

Sudden onset of angina pectoris should lead to a suspicion of recent or impending myocardial infarction

CASE 13. ANTERIOR INFARCTION, WITH PRESENTING COMPLAINT OF ACUTE LEFT VENTRICULAR FAILURE, AND MINIMAL COMPLAINTS REFERABLE TO THE CORONARY CIRCULATION

The patient, a 63 year old woman, was seen during an acute attack of pulmonary edema *In the course of the preceding year she had*

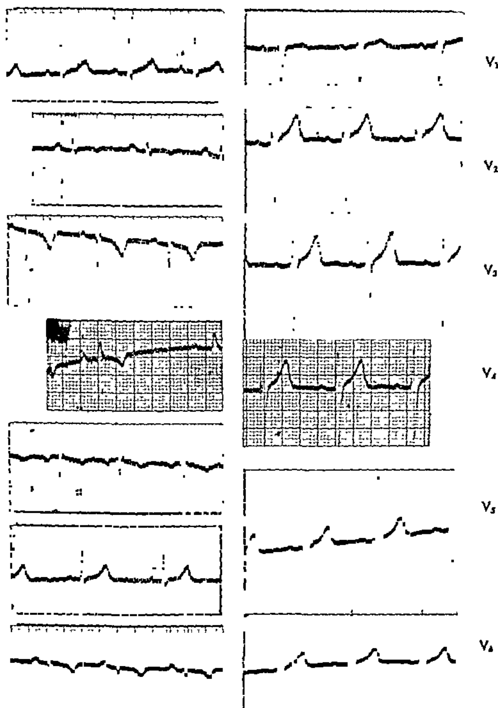


FIG 66

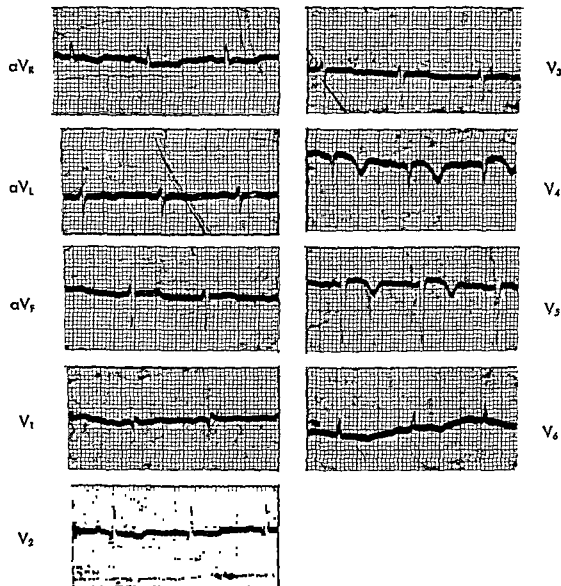


FIG 67A

had moderate but increasing dyspnea on climbing stairs, except for mild precordial pain 3 days before the onset of the pulmonary edema, there were no other symptoms suggesting myocardial infarction

Digitalization and dehydration therapy were successful. The patient suffered no cardiac pain during her 4 week hospital stay. There was no history of hypertension, and her blood pressure remained at about *120/80* When discharged from the hospital, the patient was free of symptoms.

After remaining well for about a year, the patient began to manifest gradually increasing heart failure. She died rather unexpectedly about 3 years after the onset of her illness

The first ECG (Fig. 67 *A*) was taken on admission to the hospital It showed gradual involution, at 3 months it was stabilized and no further changes occurred until the end (Fig. 67 *B*). Postmortem examination disclosed· (*1*) advanced sclerosis of all the *coronary vessels,* (*2*) *one old occlusion in* the anterior descending artery; (*3*) an old, large anterior wall infarct involving the apex, the anterior portion of the septum, and the

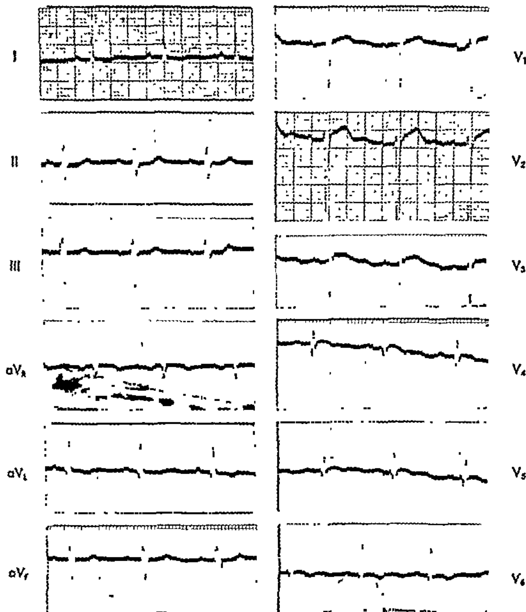


FIG 67B

distal anterior wall of the left ventricle, and extending to the left border

The noteworthy feature of this case is the paucity of symptoms suggesting myocardial infarction

CASE 14 ANGINA PECTORIS, RIGHT BUNDLE-BRANCH BLOCK (WILSON BLOCK) WITH ANTEROSEPTAL INFARCTION

The patient is a 53 year old obese woman with *mild hypertension* working as a demonstrator of cosmetics in department stores throughout the country. About 2 years before the first ECG was taken she became aware of a "burning" sensation under the left breast which radiated toward the left shoulder, this occurred whenever she was under emotional stress Each demonstration was accompanied by this anginal pain. The ECG obtained when she finally sought medical advice was entirely normal An exercise tolerance test resulted *in marked depression of the S–T segments in*

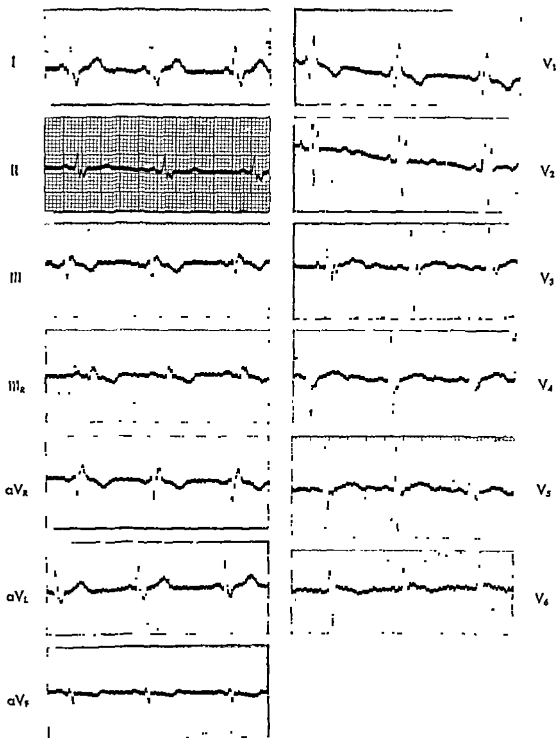


FIG 68

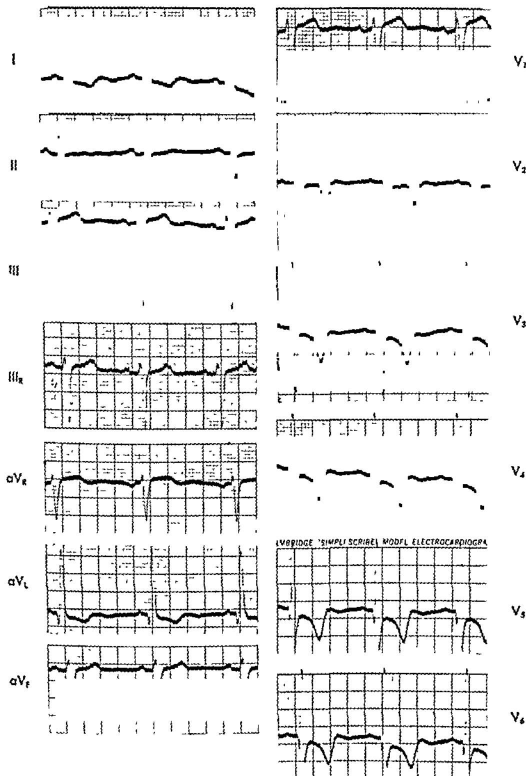


FIG. 67

leads I, V_4, and V_6, indicating coronary disease.

About a year later, while working in the Middle West, the patient had a severe attack of precordial pain and was hospitalized for 2 months. The attending physician reported that she had a clear-cut anteroseptal infarction The ECG (Fig 68) taken 3 months later showed a wide S type of right bundle-branch block (Wilson block), the main complexes were widened, especially in the S segment in leads I and II and were widened and deformed in leads V_1 and V_2, and to a lesser extent in other leads.

The patient's symptoms are about the same as before the major attack A tablet of nitroglycerin taken before a demonstration prevents the expected pain associated with it

The features to be noted in this case are (*1*) Wilson block (wide S type of right bundle-branch block), sometimes benign, may be the landmark of a previous infarct, especially an anteroseptal one (*2*) Nitroglycerin may be successful in the prevention, as well as in the treatment, of angina pectoris

CASE 15 FRESH ANTEROLATERAL INFARCTION SUPERIMPOSED ON OLD HYPERTENSIVE HEART DISEASE

The patient was a 72 year old retired detective Hypertension had been present for many years, for the 2 preceding years he had suffered from increasing dyspnea and orthopnea A week before the ECG shown here (Fig 69), he complained of mild chest pain, according to his physician, the ECG which he took showed "left ventricular strain pattern", the blood pressure was 240/150, the limb leads resembled the leads in Figure 69, and the T waves were low but upright in all the V leads.

Crushing pain in the substernal area radiating into the left arm developed 1 week later, 6 hours later, when the ECG was taken, his blood pressure was 150/90. An hour later the patient went into severe shock, and the blood pressure fell to 50/0 Despite vigorous treatment with norepinephrine, intravenously, the patient died 12 hours later. Postmortem examination revealed (*1*) an enormously enlarged heart, (*2*) all the coronary vessels atheromatous and narrowed; (*3*) scarring of the myocardium, and (*4*) a fresh thrombus 3 cm. from the beginning of the left anterior descending artery and fresh infarction of the anterolateral surface of the left ventricle

In this case, norepinephrine failed to avert the fatal outcome

CASE 16 MINOR MYOCARDIAL INFARCTION, DEATH FROM CEREBRAL HEMORRHAGE PROBABLY NOT DIRECTLY CONNECTED WITH THE CORONARY LESION

The patient was a 36 year old, extremely obese woman who for several years previously was known to have severe hypertension with normal renal function An ECG (Fig 70 *A*) taken as part of a routine examination, when her blood pressure was 290/140, was identical with one taken exactly a year earlier

Just 2 weeks after this examination, the patient for the first time experienced precordial pain—a crushing substernal pain radiating to the left shoulder and elbow and accompanied by profuse sweating. On arrival at the hospital, her blood pressure was found to be 230/100 The next day it rose to 270/130. The sedimentation rate 36 hours after the attack was 20 mm in 1 hour, on the fourth day, it subsided to 12 mm in 1 hour The blood count and temperature remained normal throughout the course. An ECG (Fig 70 *B*) was obtained 17 hours after the pain first began, tracings obtained daily for the next 4 days were identical with it On the fifth day the patient suddenly complained of unbearable headache, her neck became stiff, and she died within a few minutes.

The cause of death was revealed by postmortem examination to be a large, destructive cerebral hemorrhage The heart was greatly enlarged (750 Gm), and the wall of the left ventricle very thick. The coronary arteries were only moderately sclerotic, except for a large plaque in the circumflex branch of the left coronary artery about 1 5 cm. distal to the bifurcation. A thrombus overlying an area of hemorrhage in the plaque apparently did not quite occlude the artery

In the left ventricle, on the anterior surface about half-way between the septum and the lateral border, there was an area of fresh infarction 2 4 cm in diameter extending about half-way through the ventricular wall from the epicardium. No subendocardial necrosis or

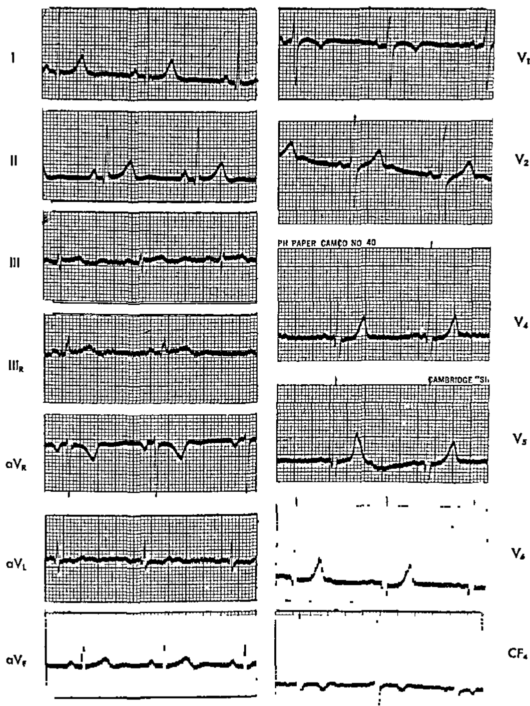

I
II
III
III_R
aV_R
aV_L
aV_F
V_1
V_2
PH PAPER CAMCO NO 40
V_4
CAMBRIDGE "SI
V_5
V_6
CF_4

FIG 70A

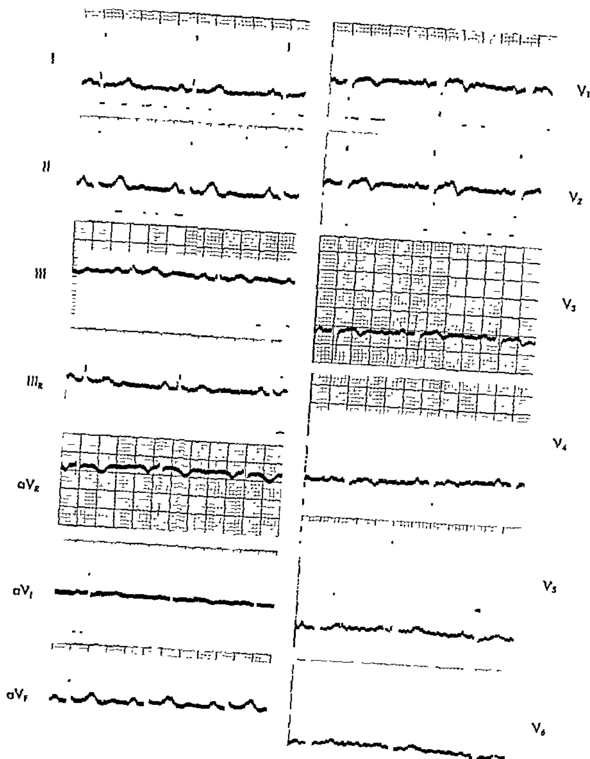
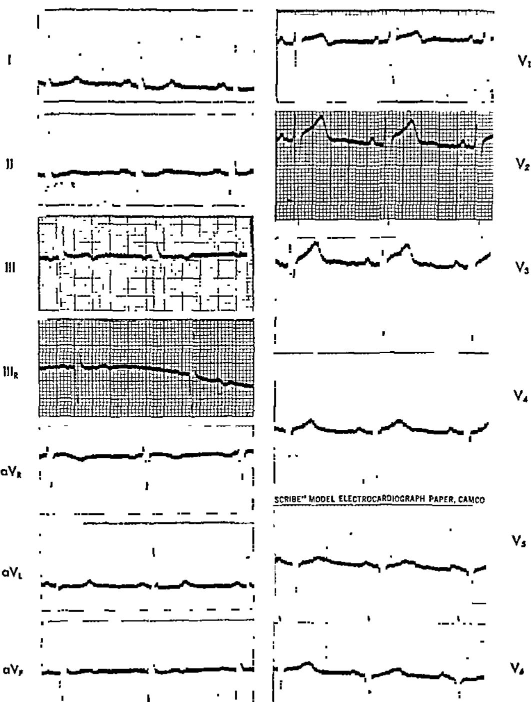


FIG 70B.



I
II
III
III_R
aV_R
aV_L
aV_F
V_1
V_2
V_3
V_4
SCRIBE" MODEL ELECTROCARDIOGRAPH PAPER, CAMCO
V_5
V_6

FIG 71

infarction elsewhere was found. There were no mural thrombi, and no evidence that a cerebral embolism was responsible for the fatal hemorrhage

The clinical features of this case fitted in well with the diagnosis of "minor infarction." Although the patient was a young woman, she was obese and had severe hypertension. The clinical story was suggestive, and there were T wave inversions in the precordial leads, as well as a slight rise in the sedimentation rate No anticoagulant therapy had been given

CASE 17. MAJOR POSTERIOR WALL INFARCTION, PULMONARY EMBOLISM

The patient is a 50 year old tailor with normal blood pressure He had a major posterior wall infarction 2 years ago which produced electrocardiographic changes for about 3 weeks. Since then, all tracings have been identical with that of the ECG shown in Figure 71. Early in the course of his illness it was decided not to use anticoagulant therapy since the patient clearly belonged in the category of "good risk" patients. On the fourth day, in the course of routine examination, the pulmonic second sound was found to be increased, and the patient admitted that he had some sticking pain in the lower right axilla

The following day the patient complained of sudden, severe pain in the left side of the chest, he went into shock, from which he recovered after 4 hours The next day there was hemoptysis. Roentgenography of the chest showed shadows in both pulmonary fields, compatible with the diagnosis of pulmonary emboli Homans' sign was positive in the left calf, where direct calf tenderness was also found The left leg became edematous 2 days later. Anticoagulant therapy was started, and the patient made a good recovery without further embolization.

Noteworthy features in this case are (*1*) Deep Q waves in leads II and III as landmarks of old posterior wall infarction (*2*) Severe pulmonary embolism in a "good risk" patient (*3*) The sudden increase in the intensity of the pulmonic second sound, suggesting pulmonary embolism (*4*) Pulmonary emboli in the course of cardiac infarction come more frequently from the lower extremities than from the heart (*5*) Safety of anticoagulant therapy despite the bleeding from the lung in pulmonary embolism

CASE 18. CHRONIC CORONARY DISEASE; SLOW BUT EXTENSIVE VENTRICULAR WALL INFARCTION, WITH REPLACEMENT BY FIBROUS TISSUE

The patient, a 64 year old tailor, had only mild breathlessness on climbing two flights of stairs when first examined (Fig 72). His blood pressure was normal, and there was neither cardiac enlargement nor distortion of the cardiac silhouette. Although the ECG was not normal, (extrasystoles and widened and slurred main complexes in most of the leads), no definite diagnosis could be made.

In the course of the following 5 years, no change to speak of was found in the ECG taken repeatedly; clinically, there was gradually increasing heart failure, edema of the legs, and a few rales at the bases of the lungs. The cardiac failure became more pronounced in 1955, and auricular fibrillation set in. The lungs were intensely congested, and the roentgenogram revealed a somewhat enlarged heart Despite vigorous treatment, the patient died in cardiac failure at the age of 70

The diagnosis by the physician caring for the patient was: gradually increasing coronary occlusion, with myocardial fibrosis and ultimate cardiac decompensation This was largely a diagnosis of exclusion, since there was no history of myocardial infarction or angina pectoris In the absence of hypertension, avitaminosis, hyperthyroidism, rheumatic heart disease, or signs of pericarditis, coronary disease seemed most likely and was the diagnosis of choice. Yet, on the basis of the ECG alone, this diagnosis could not be made.

Autopsy showed the heart to be moderately dilated in all chambers, but hypertrophy to be minimal. All three main coronary branches were severely sclerotic and narrowed, and showed evidence of old occlusions. There was extensive development of anastomoses, which undoubtedly had served to sustain life. The myocardium of the left ventricle and septum was severely scarred throughout.

The tracing illustrates a common and troublesome problem Although a presumptive diagnosis of chronic coronary disease can be made in the absence of a history of infarction or angina pectoris, the diagnosis is not definitely established Even occlusion of all the main coronary vessels need not cause death, provided there is enough time for the development of extensive anasto-

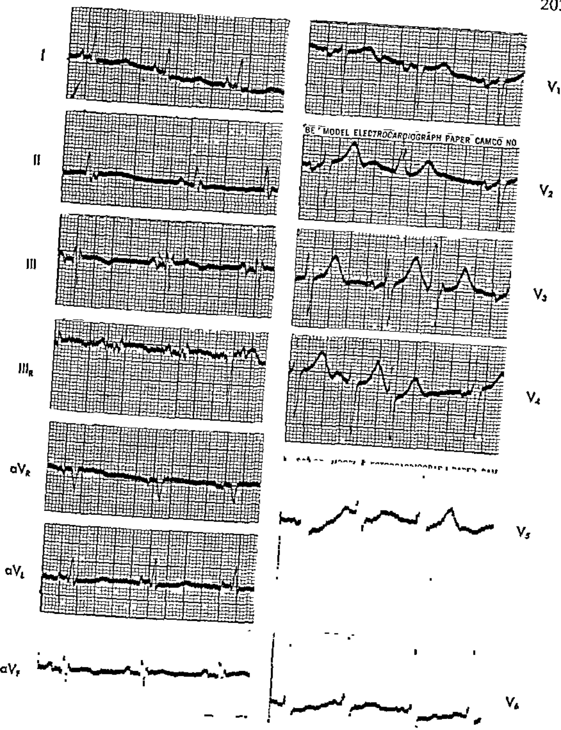

I
II
III
III_R
aV_R
aV_L
aV_F
V_1
BE MODEL ELECTROCARDIOGRAPH PAPER CAMCO NO
V_2
V_3
V_4
V_5
V_6

FIG 72

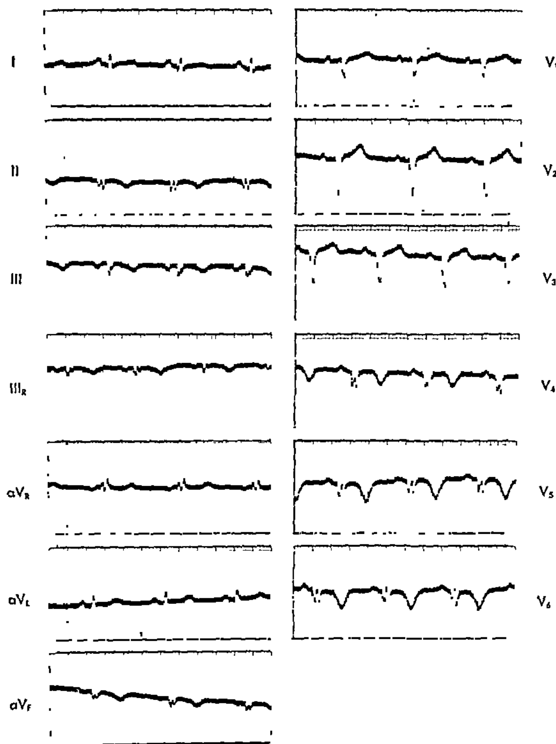


FIG. 73

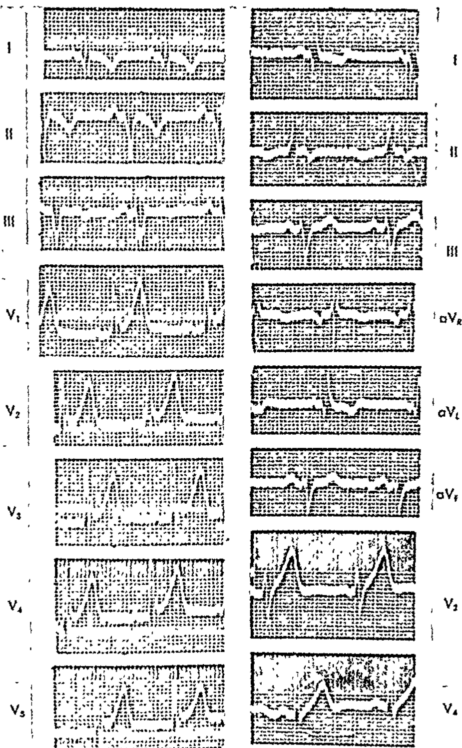


FIG. 344 FIG. 345

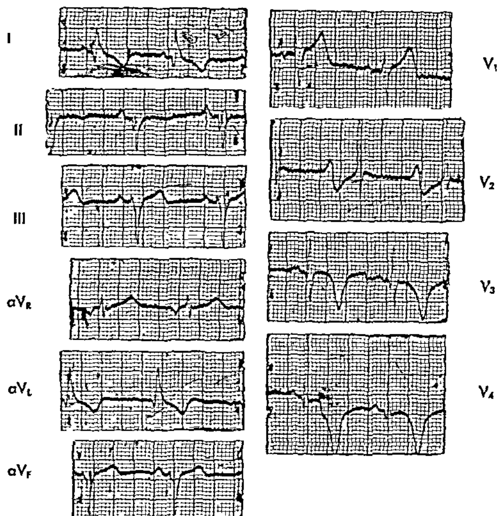


FIG 74C

moses Cardiac failure may occur in exceptional instances of coronary disease in which the cardiac enlargement is minimal

CASE 19. CORONARY DISEASE WITH HIATUS HERNIA

The patient, a 52 year old obese bookbinder with normal blood pressure, had suffered a major posterior wall infarction 4 years previously, and a major anterolateral wall infarction 3 years later. The ECG (Fig 73) shows the residuals of both infarctions, as may be seen from the changes in leads II, III, and the precordial (V) leads For a year before the first infarction the patient had suffered from atypical angina pectoris. A hiatus hernia was discovered in the course of routine investigation, and all the patient's symptoms, even when the angina became completely typical and including the first day of the infarction, were wrongly attributed to the hernia.

Hiatus hernia and coronary disease are not mutually exclusive The more typical the angina, especially when quickly relieved by nitroglycerin, the more likely it is that the patient has both angina pectoris and hiatus hernia.

CASE 20. POSTERIOR WALL INFARCTION OBLITERATING ELECTROCARDIOGRAPHIC EVIDENCE OF EARLIER ANTERIOR WALL INFARCTION

The patient was a 50 year old grocer with normal blood pressure at the time the first ECG was obtained (Fig. 74, *A*). At that time he had been suffering from increasing breathlessness for about 3 months, with a sense of

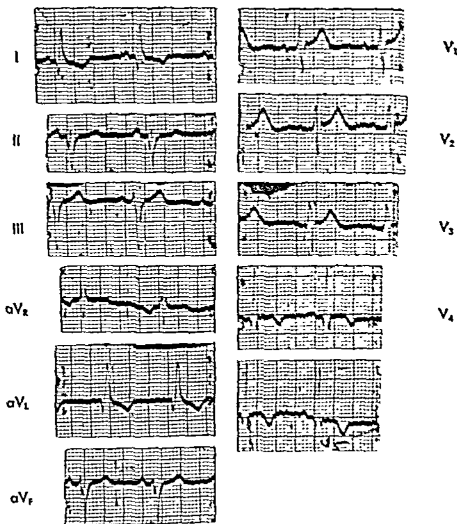


FIG 74D

substernal squeezing on exertion A typical, major anterior wall infarction occurred 1 week before tracing *A* was taken, it shows the residuals deeply inverted T wave in leads I and II, diphasic T wave in lead III, small Q wave *in lead* I, *deep*, wide S wave in leads II and III The S–T segment is somewhat elevated in the V leads, but the T waves, previously inverted in all the precordial leads, are now upright

An ECG taken 3 weeks later (Fig 74, *B*) gives evidence of improvement the T wave is now diphasic in lead I, and upright in leads II and III, the main complex in leads II and *III* is reverting toward *normal*, *the* deviation of the S–T segment in the precordial leads is less marked ECGs taken in the course of the following year were all identical with tracing *B*

A second, more severe infarction occurred 1 year later, with shock and a leukocyte count of 30,000 The ECG taken 24 hours later (Fig 74, *C*) showed evidence of anterolateral infarction, small Q waves and inverted T waves were present in leads taken from the third interspace on the left side of the chest, indicating high extension of the lateral infarct. The ECG taken 3 weeks later (Fig 74, *D*) showed the residuals of an anterolateral infarction Q waves in leads I and II and in the left precordial leads, T wave *inversion in* leads I, and V$_4$ through V$_6$

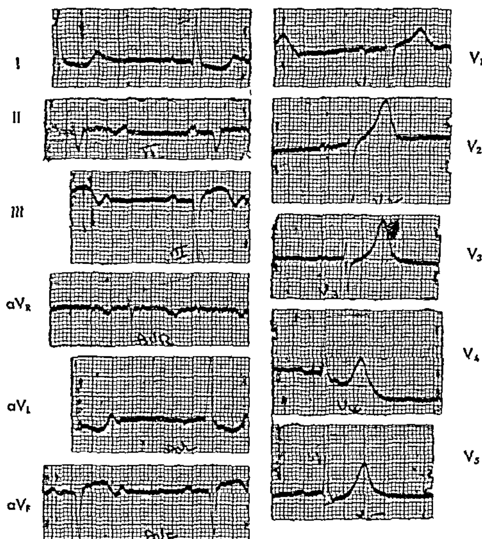


FIG 74E

The patient's recovery was remarkably good, *for 17 months after the second infarction* he had no symptoms of heart failure or of angina pectoris, although his heart, earlier of normal size, had enlarged by 20 per cent in the transverse diameter Then, he fainted while at work, was brought home, and began to complain of precordial pain The ECG taken 3 hours later (Fig 74, *E*) shows the changes of an early posterior wall infarction deep Q waves in leads *II*, *III*, and aV_F, elevated S–T segment and diphasic T waves in leads III and aV_F, reciprocal S–T segment depression in leads I, aV_L, and V_4 through V_6. *The ECG obtained 3 days later (Fig. 74, F)* shows a well-established posterior wall infarction; inversion of T waves in leads II, III, and aV_F, S–T segments at the base line *The remarkable feature of this tracing* is that all signs of the earlier anterior wall infarction are obliterated, were only this tracing available, the conclusion could be reached that the patient had recently suffered a first infarction.

Since the second infarction, the patient has had mild breathlessness, but no anginal pain. The heart is considerably enlarged to the left.

The obliteration of an old anterior wall infarction by a fresh posterior wall infarction is a clinical trap if earlier ECGs are not available *Enlargement of the heart after infarction may* occur, but is uncommon in the absence of cardiac decompensation.

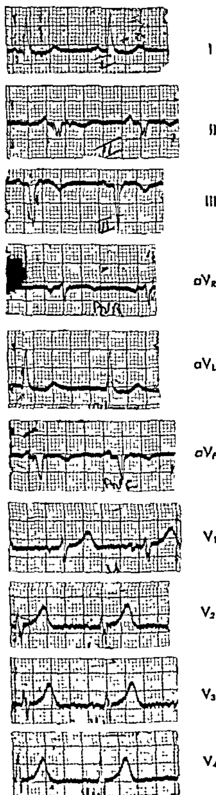


FIG 74F

CASE 21. SUBENDOCARDIAL INFARCTION MISTAKENLY DIAGNOSED ON THE BASIS OF S–T SEGMENT DEPRESSION DUE TO DIGITALIS

The patient is a 42 year old plasterer with normal blood pressure, suffering from chronic rheumatic mitral insufficiency and auricular failure. He was first seen by a local physician, who took an ECG and placed the patient on digitalis and a dehydration regimen because there were signs of some heart failure

When, 3 months later, the patient experienced nausea, vomiting, and some pain beneath the xiphoid process, probably secondary to the vomiting, an ECG was taken (Fig 75) which showed depressed S–T segments, the physician diagnosed subendocardial infarction, put the patient to bed, and called for cardiac consultation.

"Scooped-out" S–T segments should immediately suggest overdigitalization When the digitalis was stopped, the nausea disappeared and the ECG returned to its earlier appearance within 2 weeks When the patient was given excessive amounts of digitalis, the changes seen in the tracing were easily reproduced

CASE 22 AORTIC STENOSIS MISDIAGNOSED AS CORONARY DISEASE ON THE BASIS OF ELEVATED S–T SEGMENTS IN PRECORDIAL LEADS

The patient, a 34 year old salesman with normal blood pressure, suffered from some substernal pressure on exertion, but had no other symptoms An ECG was taken (Fig 76, *A*), and early myocardial infarction was diagnosed, the elevation of the S–T segment in the precordial leads was interpreted as a sign of early coronary occlusion The patient did not have leukocytosis or a fever, and the sedimentation rate was normal; nevertheless, he was put to bed ECGs taken every other day for the next 3 weeks remained unchanged Finally he was permitted to return to work, a basal systolic murmur being disregarded Occasional nitroglycerin therapy gave complete relief from the substernal pressure

Although the angina gradually increased it remained mild and the patient needed no more than 12 tablets of nitroglycerin a week at the most An ECG (Fig 76, *B*) taken 9 years after the first one showed no essential changes At this time it was apparent that aortic stenosis and an enlargement of the left

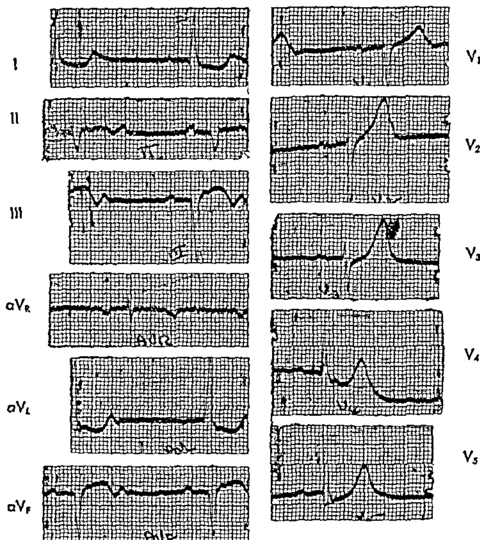


FIG 74E

The patient's recovery was remarkably good, for 17 months after the second infarction he had no symptoms of heart failure or of angina pectoris, although his heart, earlier of normal size, had enlarged by 20 per cent in the transverse diameter. Then, he fainted while at work, was brought home, and began to complain of precordial pain The ECG taken 3 hours later (Fig 74, *E*) shows the changes of an early posterior wall infarction deep Q waves in leads II, III, and aV_F, elevated S–T segment and diphasic T waves in leads III and aV_F, reciprocal S–T segment depression in leads I, aV_L, and V_4 through V_6. The ECG obtained 3 days later (Fig 74, *F*) shows a well-established posterior wall infarction: inversion of T waves in leads II, III, and aV_F; S–T segments at the base line The remarkable feature of this tracing is that all signs of the earlier anterior wall infarction are obliterated; were only this tracing available, the conclusion could be reached that the patient had recently suffered a first infarction

Since the second infarction, the patient has had mild breathlessness, but no anginal pain. The heart is considerably enlarged to the left

The obliteration of an old anterior wall infarction by a fresh posterior wall infarction is a clinical trap if earlier ECGs are not available Enlargement of the heart after infarction may occur, but is uncommon in the absence of cardiac decompensation

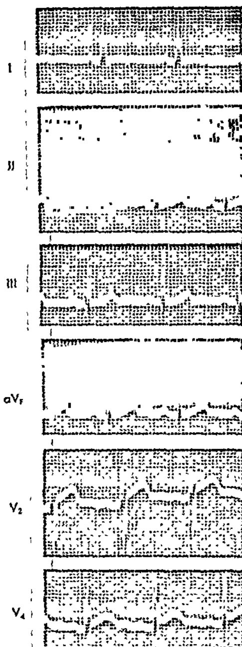


FIG 76A

ventricle were present Attacks of syncope started, and 2 years later the patient died suddenly at the age of 45

Autopsy revealed a tight aortic stenosis and a large left ventricle The coronary arteries were smooth and patent, and the entire myocardium was intact, without evidence of fibrosis or infarction

Angina pectoris which is relieved by nitroglycerin may be a symptom of aortic stenosis, and elevation of the S-T segment is not necessarily a sign of early myocardial infarction Sudden death may occur in aortic stenosis, as it did in this case.

CASE 23. MAJOR MYOCARDIAL INFARCTION AFTER MANY YEARS OF ANGINA PECTORIS AND LEFT BUNDLE-BRANCH BLOCK

The patient, a 52 year old man with normal blood pressure, had had angina pectoris since the age of 39. An ECG taken then and a year later were said to be normal Left bundle-branch block was noted on an ECG taken when he was 41, and repeatedly thereafter. The ECGs, which are not available now, are reported by competent observers to have shown "left bundle-branch block of advanced degree."

After a week of gradually increasing angina, including the new symptom of pain on smoking *one* cigaret, the patient experienced severe chest pain radiating to the left shoulder and arm An ECG was taken the next day (Fig. 77, *A*) The clinical picture of a severe infarction included hypotension, a leukocyte count of 24,000, a rapid sedimentation rate, and a fever up to 103°F for 3 days

An ECG (Fig 77, *B*) taken 6 days after the first one, and subsequent ones, all showed continuous involution The patient had returned to his usual work, with less angina than before the infarction, by the time the ECG (Fig 77, *C*) was taken 6 months after the onset

The series of ECGs show *progressive* changes The elevated S-T segments of leads II and III gradually return to normal These changes, combined with the typical course of a major infarction, were quite enough to *establish the diagnosis In the presence of* left bundle-branch block, the ECG fairly often fails to show progressive changes In such cases, the history and the laboratory features may suffice for a reasonably certain diagnosis

The noteworthy features of this case are (*1*) occurrence of a *major* infarction after many years of angina pectoris (*2*) good recovery, enabling the patient to resume his usual activities, with few symptoms, (*3*) the presence of prodromal symptoms, (*4*) changes in the ECG which, combined with the clinical course, made the

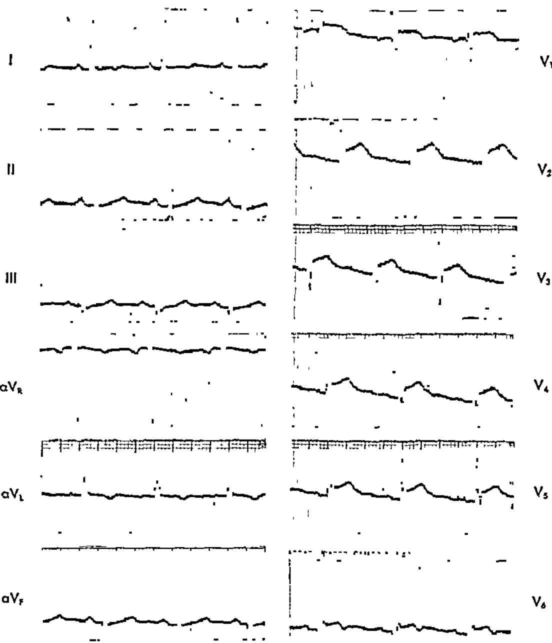


FIG 76B

diagnosis certain In this respect, the case was unusual, since in many cases with left bundle-branch block the ECG does not show the typical changes of infarction

CASE 24. ANGINA PECTORIS OF LONG STANDING, FAMILIAL HYPERCHOLESTEROLEMIA, AND INFARCTION

The patient, a 62 year old public office holder with normal blood pressure, had had mild, typical angina pectoris for about 22 years His father, 2 maternal aunts, and 4 brothers had died from "coronary attacks." The patient's blood cholesterol level ranged between 400 and 425 mg. per 100 cc, and those of a surviving brother and sister were 375 and 510 mg per 100 cc, respectively. The angina was easily controlled by rest, but when he attended legislative meetings or had to make speeches he needed an occasional

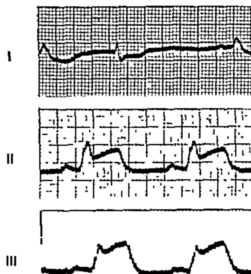


FIG 77A

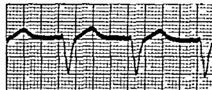


FIG 77A (Contd)

tablet of nitroglycerin. With the exception of a small, narrow S wave in leads I and aV_L, a cardiogram showed no particular abnormalities and was interpreted as being within normal limits

Engaged in a vigorous political campaign 4 weeks later, the patient noted increasing anginal pain which required several tablets of nitroglycerin daily. The pain was also more widely distributed than formerly, and for the first time radiated to the little finger of the left hand. He finally consulted a doctor in the town where he was speaking Since the ECG (Fig. 78, *A*) did not, in the physician's opinion, demonstrate an acute infarction, the patient was asked to perform an exercise tolerance test Midway in the test the patient *collapsed with severe precordial pain and* a moderate drop in blood pressure Taken to a hospital, he improved rapidly and was discharged the next day, after an ECG proved to be identical with the previous one.

The patient has returned to his normal activities, suffering from a little more angina than formerly An ECG (Fig 78, *B*) taken 1 year after the ill-advised attempt at an exercise tolerance test shows that the patient had had an anterior wall infarction, probably with posterior wall involvement

The features worth noting in this case are (*1*) the changing character of the anginal pain should have suggested myocardial infarction, (*2*) the exercise tolerance test was inadvisable in view of the history of recently changing symptoms and a definitely abnormal ECG

CASE 25. COMPLETE HEART BLOCK AND RUPTURE OF THE INTERVENTRICULAR SEPTUM COMPLICATING ACUTE INFARCTION

A 54 year old male college professor had suffered for 6 months from mild angina pectoris and bouts of nausea unrelated to exertion or to the anginal pain Roentgenography failed to show any disease of the gallbladder or of the gastrointestinal tract No abnormality was disclosed by electrocardiography, but the results of the two-step test were strongly positive Small doses of nitroglycerin completely relieved both the anginal pain and the nausea, the patient had no symptoms when he took a tablet of nitroglycerin every 4 hours on a prophylactic basis

Early one morning the patient had an attack of pulmonary edema, followed several hours later by a left hemiparesis and aphasia. He was removed to the hospital, and an electrocardiogram was taken (Fig 79, *A*) It was obvious that he had an early posterior wall infarction The following day, his condition grew worse despite all therapeutic measures, and it was found that he had a complete heart block (Fig 79, *B*) On the third day, he became more cyanotic and a murmur, previously not heard, which was loud and harsh and systolic in time, was heard to the left of the lower half of the sternum A systolic thrill was present in the same area The patient went into uncontrollable shock and died that evening. The diagnosis of ruptured interventricular septum was made during life

Postmortem examination revealed extensive atherosclerosis of the anterior descending and the left circumflex arteries The right coronary artery had advanced atheromatosis, with complete occlusion by thrombus 2 2 cm from

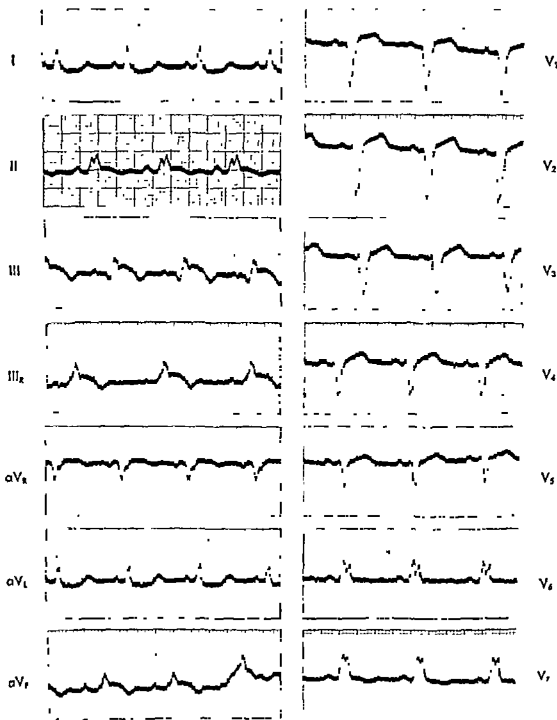


FIG. 77B

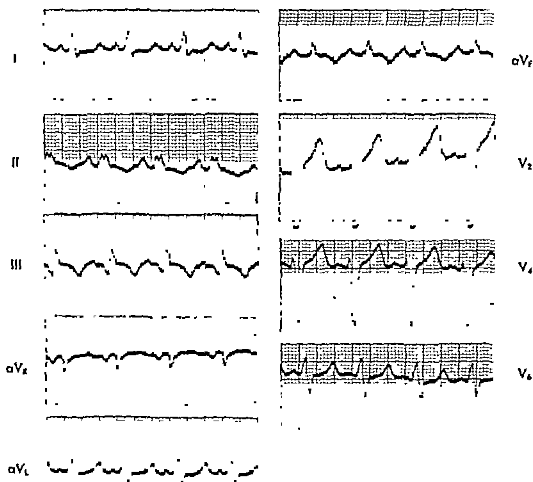


FIG 77C

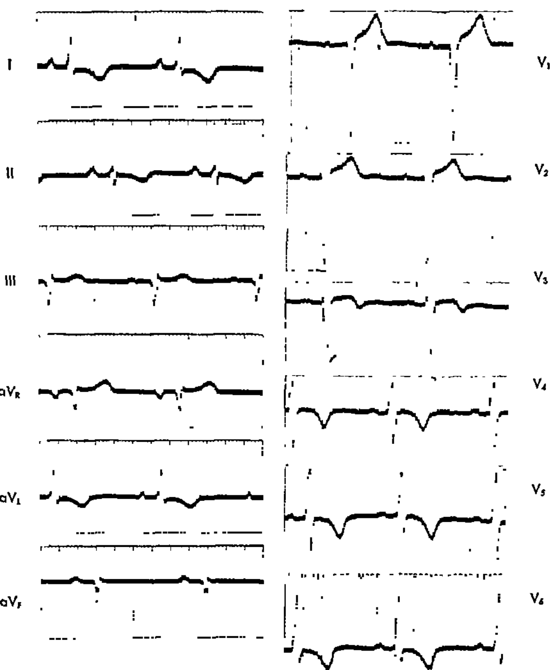


FIG. 78A

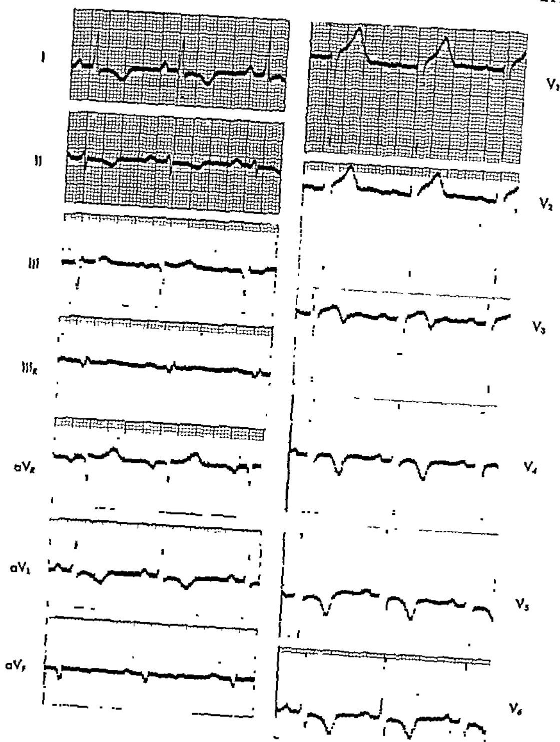


FIG 78B

its origin. The posterior wall and nearly all o the septum were infarcted. Close to the apex there was a tear almost 1 cm in diamete through the interventricular septum. The cerebral embolism undoubtedly originated fron a large mural thrombus overlying the infarcted area of the free heart wall

This case illustrates the "debut" of infarctior with pulmonary edema and cerebral embolism Complete heart block occurring during infarctior is a grave complication, and most of the patient die The diagnosis of ruptured interventricular septum was made during life in this case

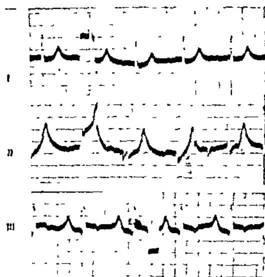


FIG 79A

FIG 79B

CHAPTER 12

Ballistocardiography and Other Diagnostic Methods

BALLISTOCARDIOGRAPHY

Ballistocardiography, although first mentioned by Gordon in 1877, is a relatively new investigative technic, the benefits of which are still not completely evaluated. Even at this early stage, it has already contributed something to our knowledge, and its promise for the future is even greater. The current state of development is comparable to that of electrocardiography before 1925: normal diagnostic criteria are being set, clinical correlations tried, technical methods corrected. At the moment, the method is empiric

Briefly, the ballistogram (BCG) attempts to assess the mechanical behavior of the body in response to the heart's impact, thus measuring the force of cardiac injection A simple example is the minute deflection of the pointer which may be observed when a person stands on a bathroom scale and holds his breath.

As Harvey[11] points out, progress has been slow because of three barriers. (*1*) Lying between the cardiovascular generator and the recording device there is a series of still mysteriously complex springs and dampers in the elastic connections through which the forces must be transmitted (*2*) The recording systems themselves are not ideal. (*3*) Most of the knowledge of the meaning of tracings has been acquired from empiric clinical correlations and not from satisfactory physiologic studies

Three general methods are in use (*1*) the high-frequency, undamped bed first described by Starr and associates[23] in 1939, (*2*) Nickerson's[16] low-frequency, critically damped bed, and (*3*) Dock's[5] direct body pick-up. The tracings obtained in these ways differ, but the main deflections are comparable, in view of this, Dock's apparatus, simple and cheap, enjoys the widest popularity

The normal ballistocardiographic complex is shown in Figure 80. In accordance with the suggestion of Starr and co-workers, the constituents of the individual complex are lettered as they are in the electrocardiogram The explanations given by Dock and the Mandelbaums[8] are

G wave: Flow into the ventricles during auricular systole

H wave: Formed during isometric contraction, as the pressure rises, the mitral valves bulge into the auricle, and the blood in the auricle is displaced headward

I wave: Footward recoil of the heart during early systole.

J wave Headward motion of the body during midsystole when the pulse wave and flow wave reach the aortic arch

K wave Formed during the late ejection phase, the footward motion is caused by the impact of the waves in the aorta, the recoil of the arch of the aorta, and the impact of auricular blood as the auriculoventricular septum abruptly ends the descent.

L wave Closure of the semilunar cusps during isometric relaxation, forcing the auriculoventricular septum toward the auricle, the impact of this blood causes headward motion

M wave Footward motion caused by the pressure of blood on the cardiac apex when, during early diastolic inflow, the auriculoventricular valves open

N wave Headward motion during early diastolic filling, the arrest of inflow causes reflux toward the auricle

A useful method of grading the abnormal

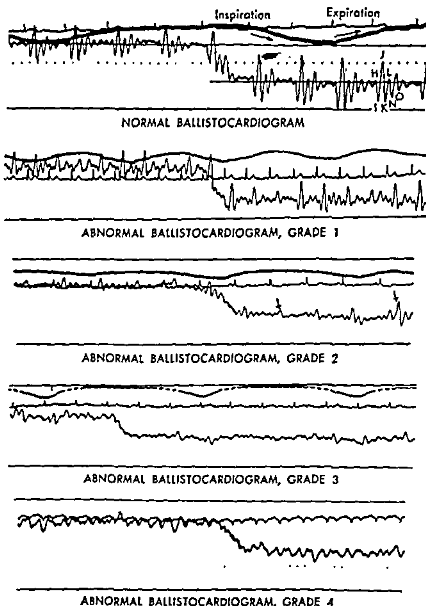


FIG 80 Normal and abnormal ballistocardiograms (From Brown et al Clinical Ballistocardiography, 1952 Courtesy of The Macmillan Co)

BCG was introduced by Brown and associates.[1] As used by Dock and the Mandelbaums, the criteria are as follows

Grade 1. More than half the complexes appear normal. The largest I–J waves are twice the height of the smallest, which may be either normal or abnormal. Changes in Grade 1 are often caused not by cardiac disease but by extracardiac conditions, such as variations in the axis of the heart, lung diseases, or splanchnic vasomotor relaxation.

Grade 2 More than half the complexes are small, the smallest perhaps less than a third the amplitude of the largest I–J wave during inspiration. Some of the small complexes may be abnormal with I or K absent or J notched Grade 2 indicates moderate circulatory abnormality.

Grade 3 All complexes are small and more than half are bizarre or unrecognizable

Grade 4: All complexes are small and bizarre Systole and diastole cannot be distinguished. Grades 3 and 4 are taken to be evidences of marked circulatory abnormality.

BALLISTOCARDIOGRAM IN NORMAL PERSONS

In persons under the age of 40, the BCG is very rarely abnormal except in the presence of heart disease. In the absence of other forms of cardiac disorder, an abnormal tracing would therefore lead the clinician to suspect coronary artery disease Borderline tracings, most of which consist of tracings that are normal in inspiration but not in expiration, must be interpreted with even greater caution.

After the age of 40, the percentage of "abnormal" tracings increases with age until the eighth decade, in which very few "normals" are found Changes in the coronary arteries are responsible for much but not all of this shift. Other factors are changes in the aorta, presbycardia, and changes in the physical properties of the body. There is no correlation between the serum cholesterol concentration and BCG changes[25] However, there may be such changes (and anginal pain) at the height of alimentary lipemia.[14]

Abnormalities in the BCG of older individuals, therefore, are not necessarily evidence of disease, at least not of clinically significant cardiac disease. However, abnormalities found within a short time after a normal tracing assume far more significance, exactly as in the case of the electrocardiogram. In all probability, most changes (Grade 2 or more) in the absence of heart failure or other varieties of cardiac disorder, are truly the result of coronary disease

BALLISTOCARDIOGRAM IN CORONARY DISEASE

Possible abnormalities in coronary disease are: (*1*) H wave of amplitude equal or higher than that of the J wave (early M type), (*2*) absence of J wave; (*3*) M-shaped J wave at its peak (late M type), (*4*) J wave late in systole, and deep K wave (late downstroke type), (5) H–J interval longer than 0 29 second, (6) L wave and afterwaves accentuated, and (7) upward bowing of the J–K segment[15]

The changes in the BCG in coronary disease are being studied in detail in many centers, notably by the group[19] at the Johns Hopkins Hospital The latter find the same trend to an increasing percentage of abnormal tracings with advancing age as among normal people Nevertheless, the overall percentage, considering all ages, of impaired tracings is 75 per cent of the coronary group and 25 per cent of normal persons The percentage of distorted records is the same in patients with angina pectoris as those with known infarction. Improvement in the tracing, after acute infarction usually, but not always, correlates with clinical improvement The newer, long-acting dilating drugs improve the BCG somewhat; estrogens and low-fat diets also seem to improve it slightly

The Johns Hopkins workers agree with the general view that the results of ballistocardiography do not constitute an accurate or completely useful method for differential diagnosis of coronary disease They are searching for methods of improving the test's usefulness, especially by using stress technics

Exercise Test The two-step exercise test gives somewhat fewer positive results than the same test in electrocardiography. Sometimes one method is positive and the other not. At any rate, they find the correlation too low for the exercise test in ballistocardiography to be considered useful The discrepancies with the anoxemia test are even wider.

Cigaret Test The Johns Hopkins investigators believe the best stress test to be the one using cigaret smoking, as proposed by Dock and the Mandelbaums. A positive test consists in a deterioration of the BCG tracing within 5 minutes after smoking a standard cigaret In one series, 60 per cent of the coronary patients were positive, against 7 per cent of normal subjects, this ratio of nearly 9 to 1 is much more impressive than the 3 to 1 ratio for the exercise test In another series, the percentage was 53 per cent as against 26 per cent.[17]

The effect of smoking on the BCG is curious and important Levy and associates first studied this effect, and noted an increase of rate and cardiac output Dock and the Mandelbaums report that smoking never "improves" the BCG tracing, although it may increase the amplitude of systolic waves in normal or hypertensive persons. Changes are produced by "denicotinized" cigarets, filter-tipped brands, snuff, chewing tobacco, pipes,

and cigars, as well as by ordinary cigarets. Cigarets made from a tobacco selectively bred to be practically free of nicotine do not influence the BCG.

Some normal subjects show BCG abnormalities after smoking; in older persons, this may indicate occult cardiac disease. Dock and the Mandelbaums state that a negative smoking test in coronary patients over 40 years of age is rare, usually a normal tracing becomes abnormal or minimal deviations from normal are accentuated Figure 81 shows the

more often than it does the ECG. However, coronary and peripheral arteriolar constriction and pooling of blood in splanchnic veins are probably important factors The effect of smoking on the BCG is reviewed in detail in Chapter 5.

Another method of evaluating the effect of stress on the BCG is to take the test after a meal. Changes may be noted, but they are not as constant or as frequent as after smoking, there is little value in the use of the postprandial tracing.

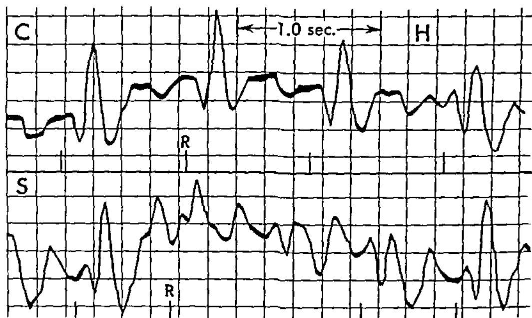


FIG 81 Ballistocardiogram in cigaret test C, Control S After smoking half a cigaret the head foot BCG recorded as displacement of the shins The first and last complexes in control are normal during inspiration on smoking other complexes show short I and J waves and a large headward wave in middiastole R, Vertical bars

typical changes in the BCG of a normal man of 38 whose response to the smoking test had been positive for 5 years

The causes of the changes induced by smoking are not clear It has been suggested that the effect is mediated through the posterior pituitary gland and the secretion of pitressin, which can produce extreme changes in both the BCG and ECG In Dock's opinion, this explanation is probably not the correct one, the rapidity with which changes in the BCG appear after a few puffs leads him to infer a direct effect on the myocardium He also thinks it unlikely that most of the effect is directly due to cardiac ischemia, since smoking affects the BCG adversely far

BCG IN ANGINA PECTORIS The BCG is more likely to be abnormal in angina pectoris than the ECG Figure 82 shows the BCG of a 46 year old man with mild angina of 3 months' duration, the ECG, including the exercise test, was normal Dock and the Mandelbaums found normal tracings at rest in only 11 per cent of 224 patients with angina, after exercise the figure decreased to less than 1 per cent This emphasizes the fact that angina (in the absence of valvular disease or severe anemia) results from coronary narrowing, which in turn results in myocardial scarring. Ballistocardiographic studies have revealed a fact that has not been generally recognized—myocardial scarring

impairs the contractile power of the heart. This impairment can be identified by the BCG. Indeed, impaired pumping function of the heart, as indicated by the BCG, is seen more often in the patient with angina pectoris than in the patient who has a well-healed infarct without angina

In most cases, the clinician who is adroit in obtaining the history and uses the ordinary methods The importance of using proper technics cannot be overestimated Displacement, velocity, and acceleration curves are all useful, the last being probably the most useful of all (Fig 83).[21]

BCG IN ACUTE INFARCTION Usually, the BCG is very abnormal (Fig 84). In most instances, Grade 3 or 4 changes are found,



FIG 82 Ballistocardiogram in angina pectoris A, Control, B, after 3 puffs on cigaret, C, after finishing cigaret R, Vertical bars The I wave is short in A, the I-J segment is very small during expiration in C This effect is more striking, as here when a habitual smoker takes his first few deep "drags" after 2 hours without a cigaret, and diminishes after he smokes less quickly at the end of the cigaret

tools of his profession needs no further help in making a diagnosis of angina pectoris In some situations (such as medicolegal cases involving insurance or industrial claims) in which a history may be prejudiced, the further help of a properly evaluated BCG may be invaluable.

In a small minority of cases with true angina pectoris, the BCG is normal So small a portion of the ventricular wall may be involved that the function of the heart is normal as far as can be ascertained by present

often with fused H-J and notched J waves Rarely, the BCG may be normal at intervals or throughout the course of the illness

After recovery from the acute episode, the BCG may remain abnormal or improve to a varying degree, in some cases to normal In general, the more severe the change, the worse the prognosis, but the correlation is not always close In 3 cases I have seen a normal BCG in patients recovering from major infarction followed by another infarction within 6 months. Patients in whom some degree of

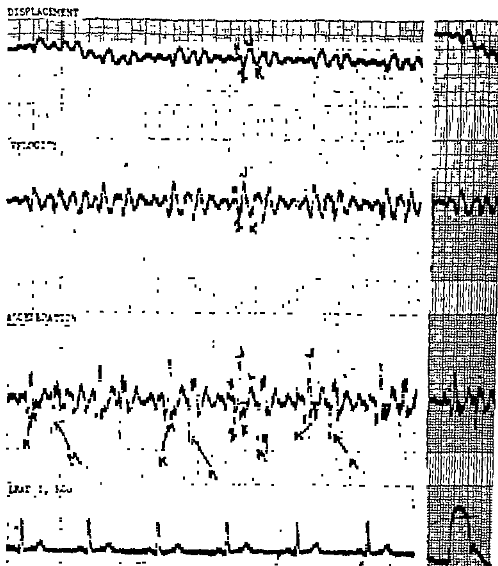


FIG 83 Ballistocardiogram showing marked abnormality on the acceleration curve which is absent on the displacement curve (From Smith et al [21])

cardiac failure or angina remains usually have abnormal tracings Figure 85 is the BCG of a 45 year old man 3 months after an acute posterior wall infarction. If the systolic components of the BCG are very abnormal but the diastolic ones are normal, it is very probable that the heart wall is badly scarred but that there is little or no decompensation.

What has been said thus far applies to the BCG taken in the supine position with the apparatus already described Other methods have been used to increase the usefulness of the BCG: (*1*) Taking the tracing in varying directions (vectorballistocardiography); (*2*) distinguishing between acceleration and displacement tracings; and (*3*) using newer technics.

(*1*) Vectorballistocardiography i e., multidirectional tracings using vector principles, is a logical development of ballistocardiography Several investigators have used this refinement. The subject has recently been reviewed by Dock,[4] who describes his own technic for the simultaneous recording of head-foot, dorsoventral, and lateral tracings He believes that this increases the value of ballistocardiography. Changes due to tortuosity of the aorta may be distinguished from those due to

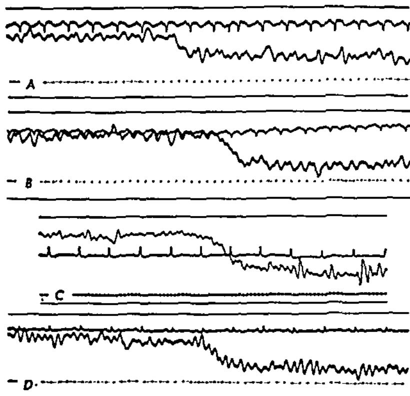


FIG 84 Ballistocardiogram in acute infarction Top, No respirations record A, Tracing of 49 year old man with a 1 day old anterior coronary occlusion, note low amplitude and irregularity of the complexes B, Same patient, 45 days later, output is very low and complexes have become more irregular and indefinite, an indication of poor myocardial recovery C, Tracing of 82 year old woman 2 weeks after posterior coronary occlusion, note very low output and irregularity and indefiniteness of the pattern D, Same patient 4 weeks after occlusion; tracing remains irregular and indefinite, but shows some improvement in amplitude (From Brown et al., Clinical Ballistocardiography, 1952 Courtesy of The Macmillan Co)

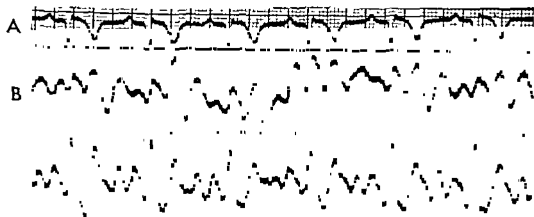
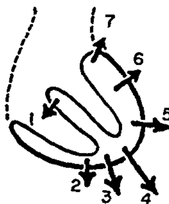


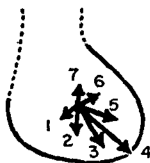
FIG 85. Ballistocardiogram in residual heart failure after infarction A, Lead II of ECG; long P R interval and a Q_3T_3 pattern also present in leads V_3 through V_5. B, Head foot tracing from the shins, one normal complex, the second, may be seen Large H and small J waves are seen in patients with gallop rhythm following the P wave in the presence of latent left ventricular failure

myocardial weakness, and large diastolic waves resulting from the gallop phenomenon or auricular systole may be detected in the lateral plane and missed in the conventional vertical BCG.

Ernsthausen and associates[4] have described a "torsion" BCG aimed at recording the







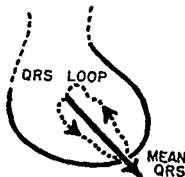


FIG 86 QRS vectors of the heart A, Each QRS vector is directed perpendicularly to the surface of the region where it is generated, the T vectors have a similar direc- [illegible]

vectors from B are drawn as if they all originated at the same point, the relative zero point of the electric field in the frontal plane D, Pathway of terminus of QRS vectors from instant to instant in a single QRS cycle (QRS loop), and the mean of the instantaneous vectors (mean QRS vector) as projected in the frontal plane of the body (From Grant and Estes[9])

rotational movements of the body Wilkins[26] has described a tilting ballistocardiograph for taking tracings in the horizontal, upright, and head-down positions. Little has been reported so far about the clinical application of the procedures in coronary disease.

(2) The BCG may be taken in such manner as to measure (*a*) displacement, (*b*) acceleration, or (*c*) velocity. Smith[20] feels that acceleration curves are more useful than either displacement or velocity in demonstrating the abnormalities of coronary disease. More investigation is needed to be sure of this

(*3*) Newer methods for taking the BCG are being tried to improve the accuracy of the test and its clinical usefulness Of these, the most promising is the mercury bed now in use at the Johns Hopkins Hospital.

VECTORCARDIOGRAPHY

Use of this new approach to understanding the heart is still largely confined to specialists. Most physicians and medical students, with

a characteristic aversion to higher mathematics and physics, have avoided the subject, considering it as esoteric and mysterious as their predecessors in the last generation regarded electrocardiography. Actually, the vector-

problems. How fruitful all this will be in terms of bedside practice is still not known, but it is apparent already that "thinking in vector terms" can throw enormous light on previously shadowy areas of cardiology,

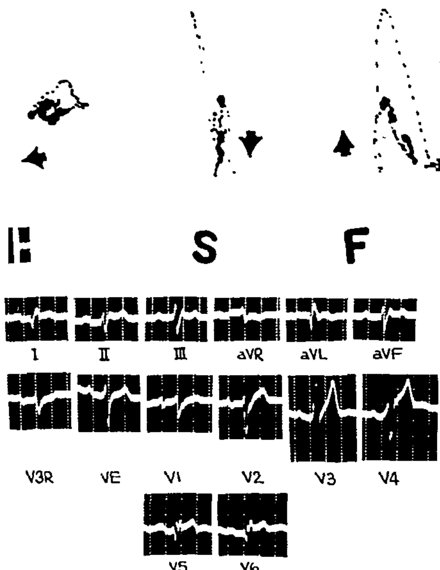


FIG 87. Old infarction of anterior and posterior walls and septum, diffuse fibrinous pericarditis (uremic), fresh apical ischemic necrosis, and left and right ventricular hypertrophy A, Vectocardiogram B, Electrocardiogram (From Wolff [27])

cardiogram (VCG) is now passing through the same phase of investigation as that which the ECG encountered 30 years ago. Basic principles are being formulated, technics standardized, tracings correlated to clinical

especially electrocardiography. The concepts are simpler than those involved in understanding the ECG, and should come first. There is nothing mysterious about the basic mathematics involved and only an understand-

ing of elementary electrical physics is necessary. Whether or not the VCG becomes a useful clinical tool, it is probable that the teaching of cardiology will soon be based on vector principles

A vector is a quantity which has size and direction Any force—mechanical, chemical, or electric—can be shown by a vector if

The QRS complex of the heart is a "depolarization" process, roughly analogous to the discharging of a condenser. The T wave represents a process of "repolarization," analogous to the charging of the condenser plates. Figure 86 shows how, as the QRS complex spreads over the myocardium, it generates innumerable QRS vectors from each

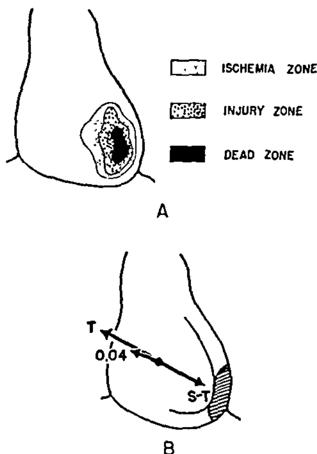


FIG 88 Vectorcardiography in myocardial infarction A, The three disturbances of electric processes which accompany acute myocardial infarction B, Abnormal vectors in acute myocardial infarction, as projected on frontal plane of body, 0 04 vector of QRS loop and mean T vector both point away from site of infarction while mean S-T vector points toward site of infarction (From Grant and Estes [9])

its magnitude and direction are known The vector is usually portrayed by the mathematical symbol of the arrow. It has three characteristics (*1*) *magnitude*, represented by the arrow length, (*2*) *direction of inclination*, shown by the deviation of the line from the horizontal or vertical, (*3*) *"sense,"* indicated by the arrowhead or caret, showing the direction in which the force is going; in the case of an electric vector, it is the orientation of electric positivity of the force.

region The ECG measures the "instantaneous spatial QRS vector" which is the resultant of all vectors generated at a given instant. The instantaneous QRS vectors, originating in different regions of the heart, differ in magnitude and direction during a single QRS cycle. When all these instantaneous vectors are plotted on a single graph as in Figure 86, a line can be drawn through their terminals, producing the "QRS" loop or "QRS vectorcardiogram (VCG)." The aver-

age of all the instantaneous vectors is called the "mean spatial QRS vector." The same process may be used for deriving loops for the P, S–T, T, and U waves.

These loops, which are beginning to mean more and more to us, may be derived from conventional electrocardiographic tracings. With a little experience, the loop need no longer be drawn, it becomes easy to visualize the loop in one's imagination and to benefit from the information obtained.

The recent introduction of the cathode ray oscilloscope for recording the electric force makes it possible to photograph the loop directly, as in Figure 87. This method is not too expensive for any well-equipped laboratory Any practicing physician who has a two-channel electrocardiograph or two conventional machines and obtains an inexpensive oscilloscope from an electronic equipment concern can now make use of it The beam of electrons visible as a shifting point of light on the surface of the tube can be readily photographed by time exposure with any camera A practical method for constructing such a system is described by Dower and Moore[7]

VCG IN MYOCARDIAL INFARCTION (Fig. 88)

The VCG is most useful in the diagnosis of obscure cases of myocardial infarction. In most instances of infarction, the diagnosis and localization can be made with a high degree of accuracy by the properly taken ECG. Occasionally, because of the site of the damage or the presence of complicating factors, the VCG adds important information.

The usefulness of the spatial vector, which is the resultant of many forces, resides in the fact that it is modified by any change in the magnitude or direction of its constituent forces When a sufficiently large area of the heart muscle becomes electrically inert, the loop assumes a new position because of the loss of forces contributed by that area. The QRS loop is directed away from the recording electrode, this phenomenon, like the Q wave in the ECG, is the result of the loss of electromotive forces from the involved muscle so that the remaining electric forces are directed away from that area

Ordinarily, the base line returns to zero during the S–T interval. Polarization has ended, repolarization has not begun, and there is no movement of electrons across cell membranes. As the result of cardiac injury, electric charges "leak" across the membranes of injured cells, the electric pressure thus generated is the "injury force," which produces a deviation of the base line until the leak is exhausted, the base line then returns to the zero point, where under normal circumstances it would have been throughout the interval The different rates at which this return takes place account for the different contours of the S–T segments seen in clinical infarction. This type of change indicates a severer degree of damage than does the "ischemia" pattern of T wave deviation It becomes normal sooner, too, the S–T abnormalities occasionally noted in conditions other than infarction are much more constant

"Ischemia" is the least severe of the effects noted during infarction, occurring farthest from the area of tissue death. It usually indicates a reversible metabolic state, while it is constantly encountered in major infarction, it is also found in slighter states of circulatory insufficiency In all such cases, the mean spatial vector of the VCG points away from the affected area, and T wave negativity is noted in the ECG

The VCG, which, like the ECG, is in many cases difficult to interpret, nevertheless seems to be superior to the ECG in the diagnosis of certain types of infarction, for example, combined infarction of the anterior and posterior walls and high posterior myocardial infarctions.[22]

Grant and Estes,[9] in their admirable monograph, show clearly the advantage of using vector concepts to study the ECG, even when a vector loop is not actually drawn or inscribed by an oscillograph They point out that in those cases in which infarction is suspected but the ECG fails to show diagnostic features the use of additional unipolar leads from chest regions other than those explored by the conventional leads V_1 to V_6 has been increasing "This practice," they state, "is an outgrowth of the dependence of empirical electrocardiography upon the 'Q wave' for the diagnosis of infarction It had been observed that the Q wave tends to be recorded at unipolar electrode positions which overlie or 'face' the infarcted region of the heart.

Accordingly, in those cases in which myocardial infarction is believed to have taken place but no 'Q wave' is recorded in conventional limb and precordial leads, it has been suggested that the infarction lies in such a position that none of these electrodes 'face' it Therefore, exploration of other regions of the chest is undertaken to find the diagnostic Q waves"

In their opinion, these additional leads are unnecessary, since all electrode positions on each of these deflections depends upon the vector's direction in relation to each lead's direction, the vector produces an abnormal Q wave in some leads, an abnormal R wave in others, and an abnormal flat or isoelectric initial portion of the QRS complex in those leads whose axes are perpendicular to the direction of the vector. By identifying the first part of the QRS loop and establishing its *abnormal direction, an infarcted area can* be diagnosed with certainty, although no Q

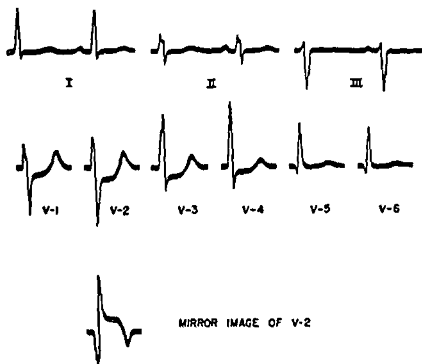


FIG 89 Electrocardiogram indicating acute myocardial infarction, in which no Q wave, elevated S-T segment, or T wave inversions occur in any of the conventional leads The infarct lies on the posterior surface of the heart, and the directions of the 0 04 vector, S-T, and mean T vectors are such that deformed R waves, depressed S T segments, and high peaked T waves are seen at V_1, V_2, and V_3 The mirror image of the deflection at V_2 shows the classic "pattern" of acute infarction (From Grant and Estes [9])

the body surface actually record from the same QRS loop. The tendency for a Q wave to be recorded at electrode positions "facing" the infarction is due to two facts (*1*) The 0 04 vector, in pointing away from the infarction, parallels the axis of that lead, and the vector therefore shows its largest deflection in that lead. (*2*) The vector is pointing away from that electrode position, resulting in a negative deflection. But since all electrode positions on the body's surface record deflections from this vector, and since the kind of deformity of the QRS complex caused by waves is present in any of the conventional leads

The vectorcardiogram shown (Fig *89*), obtained from a patient whose history and clinical picture were typical of myocardial infarction, is "diagnostic" of myocardial infarction, despite the absence both of Q waves and of T wave inversion in the conventional leads The tracing reveals no abnormalities in the QRS complex, the S-T segment, or the T wave, although the T vector is possibly somewhat smaller than normal. However, leads V_1 through V_3 show

unusually tall R waves, resulting in the earlier than normal appearance of the QRS transitional complex in the precordial leads. Furthermore, the descending limb of the R wave is slurred in these leads, a reflection of the sudden change in the contour of the QRS loop at this point. These leads also show depression of the S–T segment, and high, peaked T waves. The diagnostic features of this tracing are: (*1*) The initial part of the QRS loop is deformed, and the 0.04 vector is directed anteriorly. (*2*) T vector directed *anteriorly and parallel to the 0.04 vector.* (*3*) S–T vector opposite in direction to the other two vectors, pointing almost directly posteriorly.

The deflection at V_2, with tall R wave, depressed S–T segment, and peaked T wave, Grant and Estes point out, is the inverse or mirror image of the classic electrocardiographic pattern of infarction (deep Q wave, raised S–T segment, and inverted T wave). Since mirror image deflections are written at opposite ends of diameters through the electric field, in this patient the mirror image of V_2 deflection would be recorded in an esophageal lead or in one from the left side of the back between the spine and the scapula, and it is from these locations that this patient's diagnostic pattern of the ECG would be found.

Blind electrocardiographic exploration of the chest for Q waves, according to these investigators, may in some instances result in a false positive diagnosis of infarction. The reason for this is that such waves can be recorded from certain chest regions of some normal individuals. In empiric electrocardiography, these "normal" Q waves cannot be differentiated from those due to infarction.

PRESENT DISADVANTAGES OF VCG

(*1*) There are some technical difficulties. Special apparatus and special skills are required for using the oscillograph. With present methods, the VCG lends itself to study of individual complexes (which can be photographed) rather than to study of series of complexes; disorders of rate and rhythm can be analyzed better with the ECG.

(*2*) The VCG is not infallible even in myocardial infarction, in which it is most useful. Small areas of necrosis can still be missed, although not as often as with the ECG.

(*3*) Present methods, some hold, are crude and inexact.[13] This is a valid criticism of special technics, not of the method in principle.

(*4*) Some claim that the information provided by the VCG is in large measure also available in the conventional ECG, properly studied. This is true in most cases, and for most purposes accurate diagnoses can be made from the ECG. It is in the difficult and doubtful cases, however, that the VCG is most useful. Furthermore, the VCG makes possible the reconstruction of the ECG taken from almost any body site with a high degree of efficiency; it is therefore unnecessary to use as many leads, and time and effort are saved.

In summary, the principles of vectorcardiography are not difficult, and they can be easily grasped by anyone with a knowledge of high school mathematics and physics. An understanding of these principles immeasurably increases the accuracy of interpretation of the conventional ECG. The VCG is neither mystical nor omnipotent; the method has drawbacks and disadvantages, but it is already a useful adjunct to conventional methods, and conceivably may eventually displace them. For the moment, the absence of a vector oscillograph need discourage no one; no machine can replace the intelligent interpretation of methods now in use which yield such a high percentage of accurate diagnoses.

FLUOROSCOPY

Careful fluoroscopy of the patient with suspected coronary disease may be very rewarding. It is not difficult, with practice and attention to detail, to become expert in this method. Master and his associates have been calling attention to this for a long time and it will pay the clinician to heed their advice.

The eyes of the observer should be well accommodated to darkness. He should divest himself of the common idea that he will be seeing large excursions of the ventricular border; the movement that he sees may be as small as 1/64 of an inch. The patient should be turned slowly in all directions so that abnormalities not visible in the usual position may not be overlooked. The inferior border of the left ventricle, which is often obscured,

may be made visible if neccessary by distending the stomach by means of carbonated drinks or a *Seidlitz powder* *The patient* should be instructed to take a very short breath and hold it without strain or tension. For the purpose of timing, the outthrust of the aorta may be considered systole In difficult cases, the screen may be moved toward the observer and away from the patient Although there is some loss in light intensity, I have found that the magnification of pulsation thus obtained is valuable Newer fluoroscopic screens with much greater light intensity will probably make the task of the fluoroscopist much easier

Abnormalities in pulsation, detectable in this way, are found in about 75 *per cent of* patients who have had a major infarction, paradoxic pulsations are noted in about 50 per cent In some cases, abnormalities found soon after the infarctive episode may diminish or disappear in succeeding months.

The three types of abnormalities that may be noted are (*1*) Localized silent areas with diminution or absence of pulsation; (*2*) partial reversal of pulsation during early systole, and (*3*) paradoxic pulsation (complete reversal) The impairment of motion is usually in the lower half of the cardiac contour, most often, of course, on the left. It is seen in the usual posteroanterior position, or in a slightly left oblique position whether it is anterior or diaphragmatic In exceptional cases of posterior infarction, it may be noted only in the left lateral position. In anterior infarction, reversal of pulsation at the apex may be best visualized when the patient is rotated very slightly into the right oblique position.

LOCALIZED DIMINUTION OF VENTRICULAR PULSATION In this abnormality, the normal pulsation of the left ventricle in its lower half or apical region is reduced or absent. As Dack[2] points out, this diminution of pulsation should be localized rather than involve the entire heart border Furthermore, if this abnormality is located just above the diaphragm in an obese patient, or if it is located at the apex where there may be a pericardial fat pad, it must be interpreted cautiously.

PARTIAL REVERSAL This is limited to the early phase of systole. It is a transient *ballooning out of the involved wall followed* by a delayed normal inward movement. It lasts for at least 0 08 second, in contrast to the positional outward movement of the left heart border sometimes seen in normal persons and which rarely exceeds 0 06 second Fluoroscopy alone may be insufficient for a differential diagnosis and electrokymography may be essential. A localized transient outward movement is more likely to be the result of an earlier infarction

The physiologic outward movement sometimes seen at the left heart border may be due to traction of the heart on the great *vessels at the onset of systole, which produces* a positional movement of the heart borders superimposed on the contractile movements of the chambers.[3] It may also result from a change in the shape of the heart in early systole, this is due to early unopposed contraction of the interventricular septum before the free wall of the ventricle contracts, leading to shortening of the heart's longitudal axis and transitory outward bulging of the free walls This terminates when the free walls contract and the cardiac borders move inward

PARADOXIC MOVEMENT This is a reversal of left ventricular pulsation, in which a portion of the ventricular wall bulges out, instead of in, during systole Noted with ease when there is an aneurysmal bulge, it can also be seen, although not quite so easily, when the cardiac silhouette appears normal in contour. The upper, uninvolved portion of the left ventricle moves in as the lower portion moves out, so that the net effect is that of a scissors movement, the fulcrum being at the junction of healthy and weakened tissue

Partial or complete reversal of left ventricular pulsation is said to occur in 50 to 60 per cent of patients *after myocardial infarction*, with silent areas in 20 to 25 per cent My experience would agree with these figures, provided they are restricted to major infarction and to those cases which are confirmed by kymography. Even with the best fluoroscopic technic, what is regarded as merely absence of *pulsation in some cases is found to be reversal* on kymographic study.

Abnormalities in pulsation may be noted

early. In experimental animals, they may appear within minutes Sussman and associates,[21] with serial kymograms, found abnormal pulsation frequently in the first week, and it is almost always present by the second week if it is going to appear at all.

In the majority of cases, the disorder of motion is in the lower half of the left ventricular border. Dack[2] calls attention to uncommon exceptions: (*1*) If the infarct is large, almost the entire left border may be affected, only a small segment below the left auricular appendage remaining normal, occasionally the abnormal segment may be limited to the upper or middle segment of the left ventricular border with normal tissue beyond. (*2*) "In asthenic individuals or in the presence of left ventricular hypertrophy the apex may be covered by the diaphragm and the abnormal ventricular pulsation is exposed only during a deep inspiration In such a case one must guard against the patient straining while he holds his breath since he may perform the Valsalva maneuver which may result either in marked diminution in amplitude or pulsation or occasionally in reversed pulsation even in the absence of heart disease "

KYMOGRAPHY AND ELECTROKYMOGRAPHY

These methods are useful for graphic recording of abnormal pulsations. They confirm and supplement roentgenographic methods The electrokymogram is superior to the kymogram for recognizing old infarcts Phase analysis of the electrokymogram will often demonstrate paradoxic (outward systolic thrust) pulsation even in areas which appeared merely silent on fluoroscopy or in the conventional kymogram [12]

Sampson's[15] group in California have recently reported on the use of a portable roentgen kymograph in cases of acute infarction, their figures correspond fairly well with those quoted for fluoroscopy Deviations from normal were noted at one time or another in 80 per cent; systolic expansion of the ventricle was found in 54 per cent In posterior or posterolateral infarcts, abnormalities were observed chiefly in low and midventricular zones, in anterior lesions, the deviations from normal were more likely to extend higher. Changes in the left ventricular contraction pattern may occur very early (within an hour of the first symptoms) or may be delayed for as long as 3 weeks An increase in ventricular contraction was noted in 1 case of shock treated with norepinephrine

ROENTGENOGRAPHY

Roentgenographic study of the heart is of comparatively little value in the diagnosis of chronic coronary disease Aneurysmal dilatation may be present if there has been a previous infarction, it may appear as a localized bulge, easily seen and identified, or it may require special positioning for recognition Calcification of the myocardium should always suggest an area of old infarction Calcification of the coronary artery may be seen on the roentgenogram, by or fluoroscopy

The coronary arteries may be visualized by a contrast medium injected by catheter or still better, by means of thoracic aortography In this way, anatomic variations and other disorders of the coronary arteries may be seen

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CHAPTER 13

Differential Diagnosis of Myocardial Infarction and Angina Pectoris

THE MANY conditions which simulate coronary disease closely enough to be considered in the differential diagnosis are listed in Table 19. All except the hyperactive carotid sinus have been mentioned in the protocols of patients admitted to my service at the Kings County Hospital Errors have been made in both directions patients have been admitted with the diagnosis of coronary disease in whom one of the conditions given in Table 19 was the final diagnosis, and patients have been admitted with the diagnosis of one of these conditions and found to have coronary disease.

TABLE 19 CONDITIONS SIMULATING CORONARY DISEASE

- Pulmonary disease
  - Pulmonary embolism
  - Spontaneous pneumothorax
  - Spontaneous mediastinal emphysema
  - Tumors, thoracic and mediastinal
  - Diaphragmatic lesions
  - Pleural disease
  - Massive pulmonary collapse
- Cardiovascular disease
  - Acute pericarditis
  - Dissecting aortic aneurysm
  - Aortitis or aortic aneurysm
  - Pulmonocardiac failure
  - Acute heart failure
  - Acute rheumatic carditis
  - Valvular lesions
  - Paroxysmal heart action
  - Cardiac and pericardial tumors
  - Coronary insufficiency
- Gastrointestinal tract disease
  - Esophageal lesions
  - Gastric lesions
  - Hiatus hernia
  - Gallbladder disease
  - Acute pancreatitis

- Skeletal disorders
  - Spondylitis with radiculitis
  - Fractured rib
  - Cervical rib and scalenus anticus syndrome
  - Arthritis of shoulder joint
  - Bursitis of shoulder
  - Shoulder-hand syndrome
  - Postinfarctive chest pain
  - Hypersensitive xiphoid syndrome
- Central nervous system disorders
  - Herniated cervical disk
  - Spinal cord tumors
  - Herpes zoster
  - Brachial neuritis
  - Hyperactive carotid sinus
  - Tabetic crisis
- Miscellaneous conditions
  - Impending diabetic coma
  - Anxiety neuroses (cardiac neurosis, conversion neurosis, neurocirculatory asthenia, etc)
  - Malingering
  - Anemia
  - Thyroid disease
  - Precordial migraine
  - Caffeine sensitivity

TABLE 20. CAUSES OF ELECTROCARDIOGRAPHIC CHANGES SIMULATING THOSE OF CORONARY SCLEROSIS AND MYOCARDIAL DISEASE

Drugs and chemicals		
Atabrine	Ergot	Potassium salts
Atropine	Mecholyl	Quinidine
Digitalis	Nicotine	Quinine
Emetine	Plasmochin	Sulfonamides
Epinephrine		
Exercise		
Infections, acute	Influenza	Trichinosis
Boeck's sarcoid	*Periarteritis nodosa*	*Typhoid fever*
Diphtheria	Pneumonia	Typhus fever
Encephalomyocarditis	Pulmonary tuberculosis	Undulant fever
Hepatitis	Rheumatoid arthritis	
Metabolic, endocrine, and other disorders		
Acidosis	Gargoylism	Potassium, serum level changes
Acromegaly	Hemochromatosis	Scleroderma
Acute blood loss	Hyperventilation syndrome	Serum sickness
Alkalosis	Hypoglycemia	Thyroid disease
Artificial fever	Lupus erythematosus	Vitamin deficiencies
Carbon monoxide intoxication	Obesity	Nicotinic acid
Chronic anemias	Osteitis deformans	Thiamine
Dermatomyositis		
Pulmonary, renal, and upper abdominal conditions		
Acute glomerulonephritis	Peptic ulcer, bleeding or perforated	Pulmonary embolism
Acute pancreatitis		Uncomplicated gallbladder disease
Nervous system disorders		
Autonomic	Central	Food and ice water
Extracardiac pain	Friedreich's ataxia	Postprandial changes[4, 22, 54]
Fear	Progressive muscular dystrophy	T wave changes after drinking ice water[84]
Neurocirculatory asthenia		
Heart conditions		
Pericarditis	Fibroelastosis	Trauma
Acute rheumatic fever	Hypertension	Ventricular hypertension or dilatation, left or right
Amyloidosis	Rheumatic carditis	
Ectopic heart rhythms, especially tachycardia		
Technical errors in taking ECG		

Table 20 lists the conditions in which the lectrocardiogram is sufficiently abnormal to [illegible]

rom normal may be found in coronary disease o that this diagnosis must be considered if ny electrocardiographic abnormality is found.

Considerable attention has recently been directed to disorders of potassium metabolism, in which electrocardiographic changes may simulate those of coronary disease and cause difficulties of differential diagnosis (Fig 90). Table 21 lists the clinical manifestations of abnormal blood potassium levels. Administration of potassium salts may cause changes in the T waves and in the R–T segment which may suggest coronary disease. To avoid

diagnostic error in patients receiving potassium salts, the electrocardiogram should be taken again after stopping therapy

The problem of differential diagnosis is considerably simplified if it is constantly held in mind that the diagnosis can never be made on the basis of laboratory procedures alone, the clinical features of the case must always be appraised as well

All the conditions listed in Table 20 may simulate old myocardial infarction by ECG

The differential diagnosis may prove to be difficult if the pain is intermittent and seems to be related to exertion or movement Moreover, some of the features of true angina pectoris may be unusual, and thus be a source of confusion The location and radiation of the pain are sometimes atypical The most constant criterion, and the one which will save the physician from error most of the time, is the mode of onset and relief of anginal pain No matter how it is initiated, pain which is unrelated to exertion, emotion, or exposure to cold is almost certainly not angina pectoris Most often, when I have seen a patient with many features of angina pectoris but with atypical onset and relief, the final diagnosis has been myocardial infarction, usually minor, with atypical features While this is true almost as a matter of definition, the differentiation is of more than semantic interest From the point of view of treatment, there are the most compelling reasons for making an accurate diagnosis

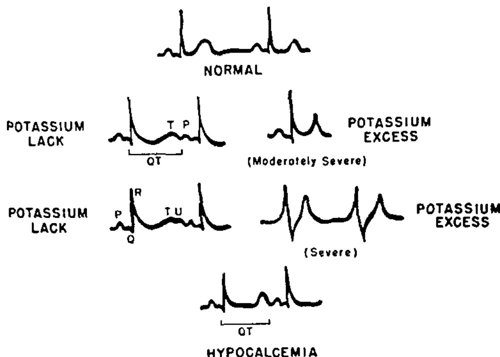


FIG 90 Electrocardiographic evidence of disturbed potassium metabolism Note flattened T waves and prolonged Q T interval in potassium insufficiency, peaked T waves and abnormal QRS complex in potassium intoxication and prolonged Q T interval without change in wave shape in simple hypocalcemia (From Talbot[55])

PULMONARY DISEASE

PULMONARY EMBOLISM

Pulmonary embolism may be confused with myocardial infarction, especially when the left lung is involved Pulmonary embolism is usually associated with bed rest (postoperative, postpartum, or in chronic illness), it may also be a complication of myocardial infarction, but does not occur on the first day. In a minority of cases, those associated with lung infarction, there may be hemoptysis

The cause of the electrocardiographic changes in pulmonary embolism has not been established Experiment has shown that coronary flow is actually increased in most

TABLE 21 CLINICAL MANIFESTATIONS OF ABNORMAL BLOOD POTASSIUM LEVELS*

Manifestation	*Hyperkalemia*	*Hypokalemia*
Neurologic and mental	Listlessness; apathy, mental confusion, heaviness of legs, weakness, hypotonia, terminal flaccid paralysis, parasthesia common, nauseau and vomiting	Listlessness, apathy, mental confusion, heaviness of legs, weakness, hypotonia, terminal flaccid paralysis; parasthesia rare, gasping (fish-mouth) breathing, nausea and vomiting
Gastrointestinal		Atonic abdominal distention, paralytic ileus
Cardiovascular	Cold gray pallor, low pulse pressure, bradycardia, faint heart sounds; peripheral circulatory collapse, sudden death from cardiac arrest	Cyanosis, wide pulse pressure, collapsing pulse, functional systolic murmurs, cardiac dilatation and failure, sudden death from cardiac arrest
Genitourinary	Oliguria and azotemia frequent	Pre-existent polyuria frequent
Electrocardiographic	Changes correlate fairly well with extracellular potassium concentration, term "hyperpotassemia" can be used without reservation, concomitant lowering of plasma sodium and calcium levels enhances ECG changes	Changes probably correlate better with low intracellular potassium concentration, which may or may not be reflected in serum potassium level, term 'hypopotassemia" applies to a potassium deficiency producing ECG changes
S-T segment, T and U waves	At potassium levels above 6 5-7 mEq L, all normally upright T waves assume characteristic church-steeple contour narrow base, steep concave ascending and descending limbs, tall pointed peak, inverted T waves of cavity origin, *e g.*, aV_R, become deeper and resemble mirror image of upright T waves; abnormally inverted T waves in epicardial leads of either ventricle may become less inverted and often upright	S-T junction shows progressive depression in leads with predominant R wave, S-T segment sags downward from depressed S-T junction in U-shaped curve, ending in low upright to inverted T wave; concurrently, U wave becomes exaggerated as one or more humps, resulting in double camel back or triple rolling contour; U and T waves tend to fuse, so that Q-T interval is apt to be measured to end of U wave, thus appearing erroneously prolonged, T and U waves are distinctive in other leads which are used for measurements

QRS complex	Characteristic changes in T wave precede QRS changes, first change occurs at potassium levels near 8 mEq/L: increase in amplitude and duration of S wave in left precordial leads at expense of R wave, at 9–11 mEq/L, intraventricular block of right bundle-branch type develops, with still higher levels, defective intraventricular conduction progresses to cardiac arrest, preterminally, QRST is fused into unusually broad biphasic sinuous curve	Usually no change, occasionally, slight widening
P wave and P–R interval	At high levels, P wave decreases in amplitude and increases to point of sinoauricular block and arrest of auricular activity, with resultant shift to ventricular pacemaker, this is irregular at first, but with increasing hyperkalemia ventricular fibrillation may occur	P–R interval may be slightly prolonged

* Modified from Myers and Talmers [44]

instances of pulmonary embolism.[62] Expansion of the pulmonary artery in cor pulmonale, it has been suggested, compresses the left coronary artery which passes between the aorta and the pulmonary artery for the first centimeter of its course [10] Naturally, if there is prolonged hypotension, there is coronary insufficiency which may go on to infarction.[31] Shock is rare in pulmonary embolism; as in myocardial infarction, there are many gradations of severity and only in severe cases does shock occur.

Other explanations for the changes in the electrocardiogram in pulmonary embolism include. (*1*) A change, possibly a pulmonocardiac reflex, in the coronary circulation [7, 44] (*2*) A vagal reflex (*3*) The pulmonary obstruction mechanically produces anoxemia which gives rise in turn to myocardial anoxemia with coronary changes [39] However, in a study of 2 cases, it was found that increasing the oxygen saturation of the blood did not affect the electrocardiogram [4] (*4*) The electrocardiographic changes are due to acute right ventricular strain produced by pulmonary hypertension [2, 40] (*5*) The changes are due to mechanical obstruction and dilatation of the right ventricle [14] These investigators found that in dogs the T wave changes of coronary involvement were inconstant and that section of either the vagus or sympathetic nerve failed to prevent changes in the electrocardiogram (*6*) The electrocardiographic changes are due to strain on the right ventricle [53]

Horn, Dack, and Friedberg[31] maintained that the changes were twofold (*1*) right axis *deviation, deep* S_I, *and normal* T_{III}, *indicating* right ventricular strain due to pulmonary artery obstruction, and (*2*) Q wave and cove planing of S–T in lead III, indicating myocardial ischemia due to shock, generalized anoxia, vagal reflex, and increased tension within the right ventricle diminishing the blood flow through the right coronary artery

Currens and Barnes[11] pointed out that a pulmonocoronary reflex has not yet been supported by experimental evidence and feel that anginal changes can be explained without postulating such a reflex. The fall in arterial blood pressure and an increase in heart rate must affect coronary blood flow. Increased right intraventricular pressure decreases the pressure gradient of blood flow to this ventricle, since approximately 92 per cent of venous return from the right ventricle emp directly into this chamber through thebesian vein.

A characteristic electrocardiographic p tern has been described.[40] (*1*) Deep S_I; (prominent Q_{III} and inverted T_{III}; (*3*) pressed $S–T_{II}$, with "staircase ascent", S- sometimes depressed, (*4*) T_{II} and T_4 n be diphasic or inverted, (*5*) occasional temporary right axis deviation.

Experience has shown that this constellati of features is found in only about 10 per c of cases When it does appear, it is high suggestive of pulmonary embolism Mo often, there is temporary right axis deviati or right bundle branch block

A study of the changes in the ECG lobectomy, when the exact time of obstructi in the pulmonary artery was known, reveal three dominant changes,[53] (*1*) in 71 4 p cent of cases there was a shift in axis to t right, (*2*) in 50 per cent there was a deep (*3*) in 28.6 per cent there was a stairca ascent of $S–T_{II}$ In a study of the ECG in cases of pulmonary embolism, the tracin were divided into four groups. (*1*) norm (*2*) nonspecific changes, (*3*) those simulati myocardial infarction, and (*4*) the changes cor pulmonale, no characteristic electrocar ographic pattern was found and those chang that did occur were transitory [56] The co clusion reached was that the diagnosis pulmonary embolism from the ECG depend on the absence of the usual changes of post rior infarction and the presence of a depress RS–T in lead I and sometimes in lead II, lo voltage shift in the electric axis to the righ and the presence in lead III of a Q wave ar inverted T. Currens and Barnes,[11] too, ho that the characteristic changes described b McGinn and White[40] are found in only a sma minority of cases. In 25 cases of pulmona embolism they found an inverted T_{III} in 21, a inverted T in lead CR_2 in 20, an S wave 1 to 4 mm in lead I in 20, a Q wave in lea III of 1 to 7 mm. in 15, a depressed $S–T_{II}$ i 11, an inverted T in lead IVR in 10, a inverted T_2 in 5, and right axis deviation 2 cases only. The importance of taking pr cordial leads is shown by the fact that in cases the only abnormality present was foun in the precordial leads, whereas in only

TABLE 22 DIFFERENTIAL DIAGNOSIS OF ACUTE PULMONARY EMBOLISM AND CARDIAC INFARCT

Diagnostic feature	*Pulmonary embolism*	*Cardiac infarct*
History	Heart disease or recent bed rest	Often, preceding agina
Onset	Sudden and overwhelming	Gradual, often, premonitory pain
Pain	Severe, often pleuritic, no typical localization	Pressing or crushing substernal radiation to shoulder or arm frequent
Dyspnea	Sudden, often intense	Mild and gradual
Cyanosis	May be severe	Mild or absent
Pulmonary second sound	May be increased	Normal
Shock	If present, precedes pain	Usually follows pain
Pulse	At onset, rapid and thready	At onset, normal or slow
Syncope	May be initial sign	Not a frequent sign
Pleural friction rub	May be present	Absent
Pericardial friction rub	Absent	May be present
Blood pressure	May be low if shock present	At onset, normal or high
Fever	Early, may reach high levels	Second or third day
Leukocytosis	Early	Second or third day
Icterus	Often present	Rarely present
X-ray	May be typical or show atypical congestion	Normal or show early congestion
Transaminase	Normal	Elevated
ECG	*See* text	Typical involutional changes

cases was the sole abnormality in the limb leads. They stated that if a tracing is taken within 24 hours of the onset, there is a tendency for the QRS complex to be prolonged

The differential diagnostic features of pulmonary embolism and coronary disease are given in Table 22 The points mentioned will assist in the diagnosis of the acute illness However, pulmonary embolism must also be considered in the more smoldering type of case; the following clues will assist in establishing the presence of pulmonary embolism [43]

1. Unexplained fever, leukocytosis, tachycardia, faintness, prostration, dyspnea, asthma, jaundice, especially in a patient with mitral stenosis or heart failure

2. Rales or consolidation in the lungs not adequately explained by heart failure or pulmonary infection

3. The periodic recurrence at short intervals of episodes that individually might be mistaken for acute coronary occlusion but which in series are much more likely to mean repeated pulmonary embolism

4 The inexplicable lack of response of a patient with congestive heart failure to therapy which seemingly should be adequate

SPONTANEOUS PNEUMOTHORAX

The sudden onset of spontaneous pneumothorax, especially on the left side, may closely simulate myocardial infarction Spontaneous pneumothorax usually occurs in younger age groups, but it occurs often enough in middle and old age to pose a real problem in diagnosis The pain may be severe, prostrating, and precordial, and be accompanied by dyspnea and cyanosis It is usually referred to the side of the chest rather than to the sternal area There is usually no fever, leukocytosis, or increased sedimentation rate

instances of pulmonary embolism.[62] Expansion of the pulmonary artery in cor pulmonale, it has been suggested, compresses the left coronary artery which passes between the aorta and the pulmonary artery for the first centimeter of its course.[10] Naturally, if there is prolonged hypotension, there is coronary insufficiency which may go on to infarction [31] Shock is rare in pulmonary embolism, as in myocardial infarction, there are many gradations of severity and only in severe cases does shock occur

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A study of the changes in the ECG at lobectomy, when the exact time of obstruction in the pulmonary artery was known, revealed three dominant changes,[53] (*1*) in 71 4 per cent of cases there was a shift in axis to the right, (*2*) in 50 per cent there was a deep S_I; (*3*) in 28 6 per cent there was a staircase ascent of $S\text{–}T_{II}$ In a study of the ECG in 50 cases of pulmonary embolism, the tracings were divided into four groups (*1*) normal, (*2*) nonspecific changes, (*3*) those simulating myocardial infarction, and (*4*) the changes of cor pulmonale, no characteristic electrocardiographic pattern was found and those changes that did occur were transitory.[56] The conclusion reached was that the diagnosis of pulmonary embolism from the ECG depended on the absence of the usual changes of posterior infarction and the presence of a depressed RS–T in lead I and sometimes in lead II, low voltage shift in the electric axis to the right, and the presence in lead III of a Q wave and inverted T. Currens and Barnes,[11] too, hold that the characteristic changes described by McGinn and White[40] are found in only a small minority of cases In 25 cases of pulmonary embolism they found an inverted T_{III} in 21, an inverted T in lead CR_2 in 20, an S wave of 1 to 4 mm. in lead I in 20, a Q wave in lead III of 1 to 7 mm. in 15, a depressed $S\text{–}T_{II}$ in 11, an inverted T in lead IVR in 10, an inverted T_2 in 5, and right axis deviation in 2 cases only. The importance of taking precordial leads is shown by the fact that in 7 cases the only abnormality present was found in the precordial leads, whereas in only 2

cardiac dullness is replaced by an area of hyperresonance. There is often accompanying pneumothorax. Subcutaneous air is often noted in the neck. Roentgenograms, especially lateral exposures (Fig. 92, *B*), demonstrate the emphysema without much difficulty. However, *if the diagnosis is not suspected, characteristic* roentgenographic signs may be overlooked.

Figure 92 shows the roentgenograms of an asthmatic child who complained of sudden severe substernal pain. The pediatrician thought that the symptoms were close enough to those of adult myocardial infarction to warrant search in her patient for atypical coronary disease. Crepitation in the subcutaneous tissues of the neck and substernal area led to roentgenographic examination, which established the diagnosis of mediastinal emphysema.

TUMORS

Thoracic and mediastinal tumors may produce sufficient cardiac pain to warrant cardiologic examination. Substernal thyroid glands have been incriminated more than other tumors.[36] Several cases have been reported in which the removal of a nontoxic substernal thyroid stopped attacks of anginoid pain. In one case, the precordial pain was fairly typical in distribution for angina pectoris and was relieved by nitroglycerin.[16] However, although there were some electrocardiographic changes, the pain was atypical in that it was not precipitated by exercise. Operation effected a complete cure. In this case, it was felt that the most likely explanation of the pain mechanism was the pressure by the tumor on the periaortic part of the superficial cardiac plexus.

Tumors of the sternum, thymus, and bronchi (especially with mediastinal extension) have all been the source of puzzling cardiac pain.

Roentgenography, which should form part of every thorough cardiac survey, will promptly reveal the presence of any mediastinal mass. Although the pain may be severe and precordial, it is almost never typical of either angina or infarction. I have seen a case of lymphosarcoma in which the diagnosis was obscure for several days because the presence of fever and leukocytosis suggested myocardial infarction.

DIAPHRAGMATIC LESIONS

Paroxysmal flutter of the diaphragm with symptoms of angina pectoris has been reported.[24, 46] The diagnosis is difficult, but if flutter is suspected, it may be established by roentgenography and phonography. A history *of encephalitis should put the clinician on* guard.

A case of trichinosis of the diaphragm simulating myocardial infarction has been reported.[5]

PLEURAL DISEASE

Tumors of the pleura, pleural effusion, and, particularly acute pleuritis may produce baffling precordial pain. Acute pleurisy, alone or in association with pneumonia or pulmonary embolism, may cause pain, sudden and severe enough to be taken for acute cardiac infarction. I have seen a case of epidemic pleurodynia (devil's grip) wrongly diagnosed as coronary occlusion.

Recurrent pain may occur as the result of chronic changes in the pleura after acute pleurisy.[47] This is sometimes accompanied by permanent degeneration of the nerves, which in turn leads to atrophy of the subcutaneous tissue in a furrow-like area over the chest wall. The pain may be mild or severe, and comes on with changes in weather, menstruation, or emotional stress. Physical signs are few, but the characteristic atrophic furrow may be found, lagging of the side, weakness of the auscultation note, and stretching sounds or fine rales on deep breathing are sometimes found.

Pleuropericarditis has been described in Chapter 9.

MASSIVE PULMONARY COLLAPSE

I have seen 3 cases of postoperative pulmonary collapse wrongly diagnosed as myocardial infarction on the surgical services. *Careful evaluation of the clinical picture and* especially of the physical and roentgenographic signs will usually establish the diagnosis without much difficulty.

CARDIOVASCULAR DISEASE

ACUTE PERICARDITIS

Differentiation of acute pericarditis from myocardial infarction may be difficult. There

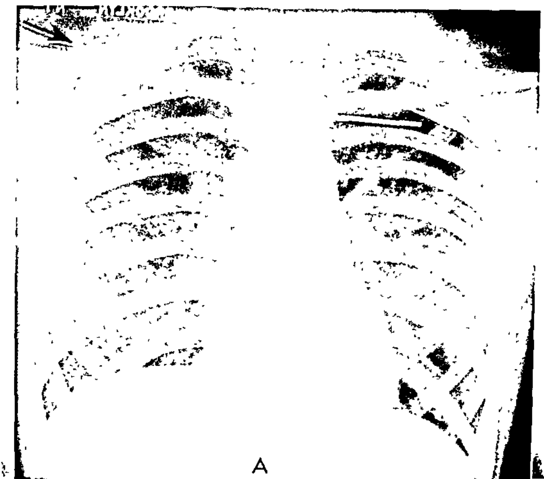


FIG 92A Spontaneous mediastinal emphysema A, Posteroanterior view, chest appears entirely normal except for a small accumulation of air in right supraclavicular region (arrow)

may be not only precordial pain but also fever, leukocytosis, increased sedimentation rate, and friction rub, the ECG, too, may simulate that of an infarction

Certain clinical features will help in the diagnosis When pericarditis follows pneumonia, tuberculosis, or rheumatic fever, one is usually on the alert for this complication. Other forms of pericardial infection, however, are not uncommon Particular attention has been called to a mild, relatively benign form which frequently follows acute upper respiratory infections.[8] The pain of pericarditis has short remissions more often than does that of coronary occlusion, although the latter pain does sometimes come and go. The pain may be substernal or even epigastric, but occasionally it is localized to a small area well to the left of these regions. It seldom is as severe or as agonizing, and it seldom radiates When it does, the radiation is usually to the shoulders, sides of the chest, or back. Exertion may produce the pain of pericarditis, but the movement is usually that of flexion or twisting of the trunk and the ache or pain may persist long after the effort has subsided In some cases, the patient may get relief from sitting up and leaning forward This posture, however, may also give relief to patients with other types of heart disease, notably, enlarged heart from any cause.

The persistence of a rather loud and diffuse friction rub favors the diagnosis of pericarditis The rub heard in the pericarditis of infarction is usually softer, more fleeting, and less widespread over the precordium.

The ECG may serve to confuse the diagnosis or to clarify it, depending on the



FIG 92B B, Lateral view air dissects out anterior mediastinal structures, identified by black line between heart and sternum extending superiorly into anterosuperior mediastinum

conservatism with which it is read and the care with which it is followed serially. There are changes in the S–T segments and in the T wave which are suggestive of coronary disease, but if suspicion is directed toward pericarditis, the diagnosis is sometimes quite clear

The typical ECG, first described by Scott, Feil and Katz[52] in *1929*, has the same contour as that seen in hemopericardium. In its most characteristic form, the S–T segment is raised in all the limb leads In other cases, these changes may be seen only in leads I and II, or in lead I alone In coronary occlusion, the S–T segment, when elevated, is convex, in pericarditis, it is curved upward or forms a straight line Early, the T waves may be high and peaked or they may be dome-shaped, sometimes they are notched. As the S–T segment sinks to the base line, T wave negativity appears,[21a] if enough tracings are taken, there is a stage at which the T wave is negative in all leads [8] The T wave may closely resemble that seen in infarction, but its inversion in all leads, without Q waves or QRS deformities, especially if the precordial leads are not diagnostic, should suggest the diagnosis of pericarditis. In the precordial leads, elevation of the S–T segment is infrequent, T wave inversion being found more often [60] For the differential diagnosis, it is important that an R wave is usually present and normal and that Q waves have not been seen over the precordium in pericarditis In subacute pericarditis, the voltage of the main complex may be low in all leads.

Pericarditis with effusion may cause such substernal oppression as to be mistaken for coronary disease

DISSECTING AORTIC ANEURYSM

Such an aneurysm is often difficult to distinguish from acute myocardial infarction Severe, possibly agonizing chest pain, leukocytosis, increased sedimentation rate, and fever may be present The pain is more likely to radiate to the back than to the arm, but this criterion is not completely trustworthy. The blood pressure usually remains at a higher level than in *myocardial infarction, but this* sign is not reliable. Moreover, in dissecting aneurysm the blood pressure may drop sharply, while in coronary artery thrombosis it may remain high, at least for some hours. The ECG may present nonspecific but confusing changes, and, when the dissection has involved the coronary arteries, may be characteristically "coronary." An ECG which remains consistently negative for several days in the presence of severe pain and fever, points strongly against myocardial infarction *The* main feature in favor of dissecting aneurysm is the discovery of evidence of dissection involving a peripheral vessel or a renal artery. Sudden obliteration of the pulse of an extremity is a very suggestive sign of dissecting aneurysm. The presence of a diastolic murmur with signs indicative of aortic insufficiency is also in favor of dissecting aneurysm. In coronary thrombosis, the pain usually starts rather mildly and works up to its maximum intensity; in dissecting aneurysm, the severest pain is likely to be very abrupt in onset Roentgenography may demonstrate a widening of the aorta; angiocardiography is sometimes conclusive but obviously can seldom be employed in acute states. The important differential diagnostic features of dissecting aneurysm and myocardial infarction are listed in Table 23.

AORTITIS OR AORTIC ANEURYSM

Either may give precordial pain which originates in the aorta and is retromanubrial and dull. The typical anginal syndrome is lacking, but with exercise the pain may become sharp and even radiate The physical signs are those usually found in aneurysm and the diagnosis is easily made, although confusion with neoplastic disease may occur. In the case of aortitis, all of the difficulties usually associated with making that diagnosis may be encountered Physical signs, history, roentgenography, the Wassermann test, must all be evaluated. When syphilitic aortitis involves the opening of the coronary arteries, the pain may be that of true angina pectoris.

PULMONOCARDIAC FAILURE

This syndrome may present features suggesting cardiac disease, even in the tendency *to sudden death* The ECG, *too, may be some*what suggestive of coronary disease. The syndrome should be suspected in cases of spinal deformity especially when there is scoliosis with the major curve to the left.

TABLE 23 DIFFERENTIAL DIAGNOSIS OF DISSECTING AORTIC ANEURYSM AND MYOCARDIAL INFARCTION

Diagnostic feature	*Aneurysm*	*Infarction*
Pain onset	More abrupt	More gradual
Radiation	More often to back	More often to arm
Blood pressure	Hypertension slightly more likely and more persistent	Less likely to remain elevated
Murmurs	Sometimes aortic diastolic	
Peripheral pulses	Often obliterated, blood pressure in arms may be unequal	Seldom affected
Hematuria	Often present early	Rarely present early
Dysphagia	Occasionally present	Very rarely present
Ocular symptoms	Temporary loss of vision possible	None
Anemia	Severe anemia possible	Rare
X-ray	Aortic widening may be noted	Localized aortic widening rare
ECG	Changes nonspecific or absent	Typical serial changes

ACUTE HEART FAILURE

Precordial pain is often a conspicuous feature of failure of the left ventricle, and left ventricular failure is sometimes noted in acute infarction These possibilities for error occur frequently, so that a correct diagnosis can be made only hours or days later, possibly only after one or more tracings have been taken Paroxysmal heart failure should be suspected when cardiac pain is felt only at night, especially when the patient is awakened from sleep. The cause of the precordial pain is still obscure The rather acute dilatation of the heart may be a factor There may be sudden coronary insufficiency, the result of increased work on the part of the heart in the presence of a coronary circulation of only border-line adequacy

ACUTE RHEUMATIC CARDITIS

Rheumatic fever may produce lesions in the coronary arteries as well as in other arteries These lesions occur fairly often but their exact frequency, and their relation to heart pain, to myocardial lesions, and to subsequent coronary disease are all still a matter of dispute But there is no doubt that precordial pain, at times very severe, may occur during active rheumatic carditis

The pathogenesis of this pain is probably complex. It may occur without obvious valvular or coronary disease The pain in rheumatic carditis, it has been suggested, is not due to aortic or coronary disease in the ordinary sense but rather to perivascular adventitial involvement In some cases, aortic insufficiency may be of paramount importance in producing the pain In other cases, the narrowing produced by pathologic changes in the coronary arteries presumably may produce enough cardiac ischemia to cause anginal pain

The differential diagnosis is not difficult The age of the patient will usually establish the diagnosis at once Active rheumatic carditis is rare after the age of 40, while coronary disease is rare before it Other evidence of rheumatic fever, such as polyarthritis, is usually but not invariably present in rheumatic carditis The onset is less likely to be abrupt, and there is often a history of previous attacks of rheumatic fever Electrocardiographic changes may be found in rheumatic fever, and sometimes the changes resemble those of myocardial infarction, the changes, however, are more likely to be atypical and rarely resemble the Q–T complex of coronary occlusion

MYOCARDITIS

Acute myocarditis may closely simulate acute coronary disease[236]

VALVULAR LESIONS

These are discussed in detail in Chapter 2.

PAROXYSMAL HEART ACTION

Severe chest pain as well as palpitations and other symptoms, may result from paroxysmal heart action. The mechanism seems clear. Cardiac work is increased and because of the shortening of diastole there is a decrease in the effective coronary flow. Coronary insufficiency occurs much more rapidly in the presence of some coronary narrowing. In a study of 125 cases, it was found that paroxysmal heart action produced precordial pain in 15 cases.[65a] The effect of possible underlying coronary disease was illustrated by the history in 12 of these cases, of previous effort angina. On the other hand, 3 cases of effort angina were observed in which paroxysmal rapid heart action did not produce angina pectoris, in these, the heart rate ranged between 124 and 140. The report cited 5 suggestive cases to illustrate the possibility that paroxysmal rapid heart action may predispose to or precipitate myocardial infarction by further compromising an already abnormal coronary circulation. In the older age groups, paroxysmal tachycardia is less often benign than it is in younger individuals. The possibility that such a paroxysm may be the result of coronary disease should be borne in mind when it occurs for the first time after the age of 40.

When the patient is seen during a period of tachycardia or irregular heart action, the diagnosis is almost self-evident, but it may be extremely difficult when the patient is *seen after an attack. In such cases, the* history is important and often conclusive; nevertheless, every effort should be made to see the patient during an attack. An ECG should be obtained if possible and in any case one should be taken during a free interval to rule out organic disease.

CARDIAC TUMORS

These may produce precordial pain. There are few helpful clues. The sudden appearance in older individuals of the signs of mitral stenosis, unexplained irregularities, and roentgenographic evidence of distortion of the cardiac silhouette may suggest the presence of a neoplasm. If primary tumor is found elsewhere, especially bronchial carcinoma or hepatoma, the diagnosis of secondary cardiac growth may be suspected.

CORONARY INSUFFICIENCY

The observation by Master and associates[42, 43] that states of coronary insufficiency were not necessarily associated with myocardial infarction and that infarction need not be caused by coronary occlusion was an important contribution to American cardiology.[20, 25, 43] This dissociation had previously been pointed out by a number of German workers.[8, 9, 13, 20, 59] Nevertheless, it was Master who forcefully brought to our attention that "coronary insufficiency" results from several causes and who demonstrated that the syndrome of "acute coronary insufficiency" is intermediate between the brief anginal seizure and the longer irreversible infarctive event. In this syndrome, the prolonged insufficiency of coronary flow in relation to the needs of the myocardium produces ischemia and pain. In some cases there is myocardial necrosis, usually in the subendocardium. In recent years, it has been recognized that acute coronary insufficiency may indicate a minor myocardial infarction or an early stage of a major one. In any event, the condition should be treated with respect and care. The salient features in the differential diagnosis of acute coronary insufficiency and myocardial infarction are listed in Table 24.

GASTROINTESTINAL TRACT DISEASE

ESOPHAGEAL LESIONS

Severe substernal pain may sometimes be caused by lesions of the esophagus. I have seen several patients in whom coronary disease had been diagnosed and in whom routine barium study of the mediastinum had later disclosed an esophageal carcinoma. Localized esophageal spasm may produce a somewhat atypical angina, but the pain is not related to exercise and rest, and there are no clear-cut electrocardiographic changes during the attack. Peptic ulcer of the esophagus may cause severe distress under the sternum. Rupture of the esophagus, because it occurs suddenly, may simulate infarction. The history, the

ECG, and roentgenography should suffice for a correct diagnosis of esophageal disorders.

GASTRIC LESIONS

One of the most difficult problems in differential diagnosis is posed by "indigestion" which may be due to lesions of the stomach, gallbladder, colon, or other organ, or to coronary disease. Each may present some of the features of the others, and they may coexist. Pylorospasm in peptic ulcer or gallbladder disease may cause pain which is felt in the chest rather than in the abdomen.[28] Distention of the stomach by water or air may reproduce this discomfort, and atropine often abolishes it. The circumstances under which the pain occurs, rather than its location or radiation, are important in the differential diagnosis. Gallbladder disease seems to occur much more frequently in association with coronary disease than in normal persons, but there is no statistical evidence of such association between coronary disease and peptic ulcer.[61] The evidence for a contrary view is unconvincing [23]

It has been pointed out that true angina pectoris of cardiac origin may occur 2 to 3 hours after a meal, and during the night at hours characteristic for ulcer pain [8] Epigastric radiation of the anginal pain may add to the confusion; radiation to this site may result from the presence of a peptic ulcer In 1 case of associated angina and peptic ulcer, successful treatment of the ulcer symptoms resulted in a remission of the anginal pain

Chest pain may be caused by diverticula of the stomach, and may be puzzling [28]

Chest discomfort is infrequently caused by "cascade stomach "[28] In this condition, there is abnormal spasm between the cardia and the body of the stomach, so that food first enters an upper pouch and then spills over into the lower stomach Usually, the complaints are few or minor, but in sensitive patients the pain may be a source of diagnostic confusion

HIATUS HERNIA

Hiatus or diaphragmatic hernia is often annoyingly difficult to differentiate from cardiac disease The type and location of the pain are of little help since in hiatus hernia the pain is usually substernal In a scholarly study of 50 patients, the pain was found to radiate to the back in 5, to the left shoulder in 12, and to the inner surface of the left arm in 16 patients [39] Pain was experienced after a heavy meal by 29 patients, and most patients reported pain upon lying down. The pain was usually described as acute, deep, and boring. Nitroglycerin even afforded relief to some patients. This could easily be a description of a slightly atypical angina pectoris. The patient with hernia, however, often has a long history of "heart trouble" (25 years or more) without any change in character; many patients, too, volunteer the information that the pain disappears when they stand A gastrointestinal examination should routinely be part of the cardiac survey of such patients The patient may have to be placed in the Trendelenburg position and asked to perform the Valsalva maneuver Hiatus hernia and angina pectoris may coexist, as in 20 of my patients, in whom two sets of symptoms required careful sorting If the patient suffers pain which is definitely related to stair climbing or excitement, true coronary angina pectoris is probably present, whether or not there is a concomitant hiatus hernia

A number of theories have been formulated to explain the mechanism of this "angina" Jones[53] believed that the pain is probably mediated by visceral afferent fibers from the esophagus and the cardiac or fundic portion of the stomach, by the diaphragmatic sensory afferent fibers contained in the phrenic, or middle or lower thoracic nerves which overflow to adjacent lower cervical or low thoracic segments The shoulder pain is largely due to diaphragmatic irritation

Figure 93 is a barium roentgenogram of a 64 year old woman's stomach, revealing a hiatus hernia For many years it was believed that the patient, despite a negative ECG, was suffering from coronary disease with atypical angina Left phrenic nerve crush gave almost complete relief

GALLBLADDER DISEASE

Since the earliest known history of coronary disease, its differentiation from gallbladder disease has been difficult This very point was in dispute in the celebrated case of John Hunter, the postmortem examination revealed the presence of gallstones and of coronary

TABLE 24. DIFFERENTIAL FEATURES OF ACUTE CORONARY INSUFFICIENCY AND ACUTE CORONARY OCCLUSION*

Diagnostic feature	*Acute coronary insufficiency*†	*Acute coronary occlusion*
Mechanism	Decreased oxygen or blood supply to myocardium, or disproportion between supply and demand, transient and slight to prolonged and severe anoxia or ischemia; often, reflex vasoconstriction	Complete occlusion of coronary vessel, complete ischemia, no reflex mechanism
Pathology	Coronary arteries normal to severely diseased, and usually sclerotic, no acute muscle changes in simple episode of angina pectoris, in severe form, focal areas of diffuse, disseminated necrosis in subendocardium and papillary muscles, pericardial or endocardial involvement absent or slight	Coronary arteries invariably diseased; massive, confluent infarction extending from endocardium to pericardium; pericarditis and frequent mural thrombosis with embolization
Predisposing factors	Arteriosclerotic, hypertensive, valvular, and luetic heart disease	Arteriosclerotic and hypertensive heart disease
Exciting factors	Effort, emotion, extremes of temperature, food, tobacco plus alcohol; valvular heart disease, anesthesia, operation, shock, heart failure, tachycardia, auricular flutter or fibrillation, fluctuating blood pressure, hypoglycemia, epinephrine, anoxemia; carbon monoxide intoxication, hemorrhage, anemia, pulmonary infarction and embolism, status asthmaticus, visceral reflexes, coitus, strain at stool, infection, trauma, thyroid disease	Possibly, operation, shock, or drop in blood pressure

Laboratory features	None in simple attack of angina pectoris; usually, moderate leukocytosis and rapid sedimentation rate if myocardial necrosis present	Leukocytosis, rapid sedimentation rate
Fever	None or slight	Constant, usually 100° to 103° F.
Pain	Slight to severe; usually relieved by nitroglycerin	Usually severe; aggravated rather than relieved by nitroglycerin
Gastrointestinal features	No nausea or vomiting in simple attack of angina pectoris	Nausea and vomiting common
Cardiovascular features		
Shock	Usually absent	Common
Heart sounds	Usually unchanged	Poor, tic-tac, embryocarditic, gallop
Pericardial rub	Absent	Present
Blood pressure	Usually unchanged, may rise during pain	Definite fall
Tachycardia and arrhythmias	Usually absent except as precipitating agent	Common after onset
Heart failure	Variable	Common, pulmonary congestion frequent
ECG	RS-T depressions, T wave inversions	RS-T elevations into T wave inversions; large Q waves; reciprocal relation between leads I and III
Degree of recovery	Complete for single attack of angina pectoris; variable otherwise	Prolonged illness and sequelae of attack for years
Prognosis	Depends on precipitating factor	Death not uncommon; residuals often permanent

* Modified from Master [11]   † Synonyms Acute coronary insufficiency without acute occlusion, myocardial necrosis or infarction without acute coronary occlusion, subendocardial necrosis or infarction

occlusion. The symptoms of the two conditions have been mistaken for each other or have been found to exist in the same patient, the latter occurs in a significantly greater number of cases than might be expected from the incidence of the two diseases. Disease of the gallbladder occurs almost twice as often in persons with coronary disease as in those with normal coronary arteries.[61] It is possible that similar metabolic faults, infections, or indiscretions in living may be factors common to both conditions.[65]

There is no reason to believe that coronary disease may cause lesions of the gallbladder, although the passive congestion which may occur in the course of heart failure may involve the gallbladder. Gallbladder disease is a fairly frequent diagnosis in the presence of the engorged liver of cardiac disease. A search for venous distention will prevent such error, although a tender, swollen liver may remain after other signs of passive congestion have subsided.



FIG 93 Hiatus hernia

There is some indication that morbid changes in the biliary tract may reflexly affect the heart or coronary circulation.[23] Anginal pain in man has been produced experimentally by dilating the common duct.[49] In dogs,

distention of the common duct resulted in electrocardiographic changes, for example, abnormalities of rhythm and conduction but only after coronary damage had been inflicted, as by ligation of even a small coronary artery.

Some 20 years ago, the prompt disappearance of both angina and electrocardiographic abnormalities was reported to have resulted from gallbladder operation in a series of cases with the anginal syndrome and inverted T waves. While this proves that removal of a diseased gallbladder may have a beneficial effect on the heart, it is not necessarily a demonstration that pathologic changes in the gallbladder cause coronary disease.[63]

In a patient with acute pain and fever, both angina and gallbladder disease may have to be considered. Vomiting and even spasticity in the right upper abdominal quadrant may be characteristic of either. The pain of heart disease may radiate to the epigastrium, but it is almost never actually centered in the right upper quadrant. It may radiate to the right shoulder, as it does in gallbladder disease, but does not radiate to the subscapular region.

The question whether to operate or not arises in some cases. Since gallbladder surgery [illegible] operation [illegible] ECGs are obtained [illegible] d the pain centers in the right upper quadrant and radiates to the right subscapular region, it is fairly safe to rule out myocardial infarction. Surgery may become necessary in a patient with known coronary disease who also has biliary tract disease. The cardiac pain may occasionally be alleviated in such cases by the removal of the gallbladder, but there is no certainty about it,[63] the added risks of operation in a patient with heart disease must be considered. Gallbladder surgery considerably benefited one series of patients, the dangers added by heart disease were believed to be overemphasized.[40] In general, the indications for surgery in patients with both diseases are the same as in those without angina pectoris, with the additional risk borne in mind.

ACUTE PANCREATITIS

It is seldom difficult to differentiate acute pancreatitis from coronary disease. Nevertheless, I have seen 2 instances in which the patients were admitted to hospital with the diagnosis of coronary occlusion. Some years ago, Dr. Caspar Burn called my attention to several instances of acute pancreatic lesions found at autopsy of individuals who had died from myocardial infarction. Since then, I have found a significant rise in the serum amylase level in a number of patients with myocardial infarction and vague abdominal pain. This occurred early in the course of the illness, and soon subsided. The serum amylase had returned to normal levels by the time the patients were ready to leave the hospital. The cause of this phenomenon remains to be satisfactorily explained.

SKELETAL DISORDERS

SPONDYLITIS WITH RADICULITIS

The intense pain which spondylitis of the cervical or thoracic spine may cause can simulate heart disease,[12] so, too, may any disease of the sensory roots of the spinal nerves or pressure upon them. If the pain is localized in a small part of the distal dermatome supplied by that root, the dermatome cannot be mapped out as an aid to diagnosis. Usually, with involvement of the fourth thoracic root, the pain extends around the thorax to the sternum at the nipple area. But if the fibrosis of the involved nerve root is of sufficient degree, the pain may be felt only in the anterior thorax or the axilla. Root pain tends to grow more severe on coughing, sneezing, straining, defecation, or lifting of heavy weights.[13] In addition, the pain is produced or intensified by any maneuver which stretches the nerve root, as, for example, stooping over without bending the knees or straight leg raising in a recumbent position. Often, too, there is tenderness to percussion over the corresponding portion of the spine. Diagnostic errors may be avoided by attention to these characteristics and by careful mapping of affected areas and of skin sensitivity.

Radiation of pain due to spinal deformities may also simulate cardiac pain.[65] Such deformities, especially exaggerated dorsal kyphosis, may be accompanied by puzzling precordial pain, some of the features, such as occurrence on exertion, occasionally short

duration, and partial relief by nitroglycerin, may suggest a cardiac origin. However, the pain is often aggravated by recumbency, with sharp pains in the back or elsewhere in the chest felt simultaneously with the precordial distress, the relief obtained with nitroglycerin is delayed, the sternal oppression is usually superficial and lacks the choking or strangling sensations of true angina pectoris Relief usually results from the use of special braces during the day and a hard mattress for rest or sleep The partial relief obtained with nitroglycerin is perplexing and misleading; in part it may de due to the psychic effect and in part to the marked vasodilation (comparable to the relief obtained when local vasodilation is brought about by physical means).

In a detailed discussion[53] of the possible pathogenesis of such pain, it was noted that the location rather than the extent of the bony changes probably determines the irritation of the spinal nerves Either abnormal straightening or marked bowing of the spinal column elongates the spinal canal; but since the spinal cord is relatively fixed and the spinal cords are essentially immobile at the intervertebral foramens, there is impingement on the nerve fibers at the foramens and tension at their connections with the spinal cord, with resultant pain The relief obtained by the use of abdominal belts[35] might thus be explained in part by the improvement in general posture

Many aspects of this interesting relationship between vertebral changes and anginoid pain would seem to require further clarification. Except in the most clear-cut cases, the utmost care must be exercised in arriving at a clinical decision The roentgenograms are suggestive but by no means conclusive, since they may show minimal pathologic features, posture or sharply localized disease may be responsible for the symptoms. On the other hand, even the most advanced spinal osteoarthritis may not be accompanied by any evidence of nerve root irritation, so that the diagnosis cannot be made on roentgenographic evidence alone The frequency with which such symptoms, when they occur, are referred to the left side, resulting in confusion with heart disease, may be explained in several ways: (*1*) Pain referred to the right side of the thorax is less important in the differential diagnosis and is therefore less likely to be reported in medical journals. (*2*) A more likely probability is that such distress, which is u ally mild, is "filtered out" of the patient's c sciousness, whereas pain in the cardiac reg is more likely to send him hurrying to physician. (*3*) Most important, although le frequent, are the cases with coexisting ne root irritation and cardiac disease. In su cases, the heart disease may determine t location of the nerve root pain, at least in far as it is consciously perceived, or the p may act as a trigger mechanism initiating t angina pectoris. I have seen at least 2 ca in which this explanation seemed to app the pain started in the back when the pati was at rest, changed to precordial press within a few seconds, with radiation to the l arm, and was immediately relieved by nit glycerin. Investigation revealed that there w both spinal nerve irritation and severe my cardial injury. Both patients also suffered fr true angina of effort.

Figure 94 shows spondylitis of the cervic vertebrae in a 55 year old man who co plained of pain in the precordial area. Exe tion increased the pain, so that angina pecto had been diagnosed several times The roe genogram clearly shows that in addition to t anterior "lipping" there was also posterior i volvement The latter is probably of great clinical importance, since it is there that t posterior roots emerge

Occasionally, coronary disease may be a companied by muscle spasm and cutaneo hyperesthesias and paresthesias which a often atypical, these may lead to the mistake diagnosis of a skeletal disorder.

FRACTURED RIB

Especially when near the precordium, fractured rib can be confused with cardia infarction. This is particularly true if t initial blow was minimal or has been forgo ten, or in cases of so-called spontaneous fra tures after coughing or exertion A patie with asthmatic bronchitis fractured a rib aft a severe attack of coughing, before the corre diagnosis was established, cardiac disease wa considered as a possibility. Another example the case of a 53 year old man who was a mitted to the hospital with the diagnosis "coronary thrombosis"; localized tendernes almost unknown in myocardial infarction, le to the correct diagnosis. The patient had struc a bedpost the previous night after a convivia



FIG 94. Cervical spondylitis (See page 254)

evening, but had forgotten the incident. Figure 95 shows his broken rib

CERVICAL RIB AND SCALENUS ANTICUS SYNDROME

Atypical precordial pain may occur in ... tions[60] The ... volved in ... ontaneous pain in the chest, neck, shoulder, or upper extremity, tenderness over the brachial plexus, signs of venous obstruction, and vasomotor changes The following maneuver will aid the diagnosis of the two syndromes "The patient sits with arms extended horizontally at the

... that the ... rotated as far as possible ... away from the side being tested A positive result is indicated by marked diminution of, or complete disappearance of, pulsations in the radial artery as determined by the physician's fingers"[15]

Some believe that the scalenus anticus syndrome may follow cardiac infarction The basis may possibly be spasm of the scalenus anticus muscle as a sensorimotor complex caused by referred pain in the sensory distribution of cervical segments 3, 4, and 5[11]

Roentgenography will establish the presence of a cervical rib, and the maneuver described



FIG 95 Fracture of rib (arrow) which caused pain simulating coronary disease

ve makes possible the diagnosis of both dromes. The diagnostic features of coro-y disease are usually absent In a case of ateral cervical rib (Fig 96), the patient ffered from bilateral pain; both the patient d his physician wrongly interpreted the pain n the left side as cardiac in origin.

develops within 6 months after a myocardial infarction,[15a, 17, 45] The syndrome is in some respects analogous to the shoulder-hand syndrome. Occurrence of the pain disturbs both the patient and the physician, and has frequently aroused suspicion of angina or recurrent infarction Fatigue often increases the

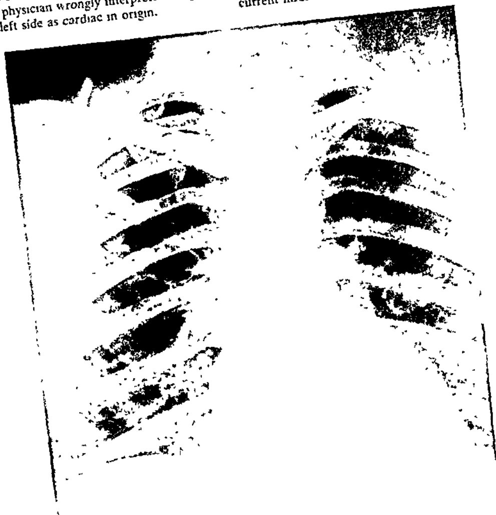


FIG 96 Bilateral cervical ribs

discomfort, and tender spots in the muscle or the overlying skin may sometimes appear.

Differentiation of this syndrome from angina may be made on the basis of the following features:[17] (*1*) The pain is not specifically related to exertion; it may occur after a trying or fatiguing day. (2) There are no electrocardiographic changes during the pain (3) The response to nitroglycerin is poor or absent. (*4*) The pain may be reproduced by arm or body motion.

Several explanations have been offered to

ARTHRITIS OF SHOULDER JOINT, BURSITIS

These may simulate the referred pain of cardiac disease, but seldom cause much difficulty in the differential diagnosis

SHOULDER-HAND SYNDROME

This syndrome is discussed in detail in Chapter 9.

POSTINFARCTIVE CHEST PAIN

In 13 to 20 per cent of patients, residual pain in the muscles of the left pectoral area



FIG 95 Fracture of rib (arrow) which caused pain simulating coronary disease

MISCELLANEOUS CONDITIONS

IMPENDING DIABETIC COMA

Precordial or epigastric pain in diabetic acidosis is often severe and disconcerting. The pain disappears upon adequate treatment of the acidosis, thus leaving no doubt about the diagnosis. Nevertheless, two disturbing features must be borne in mind. (*1*) Fluctuations in potassium metabolism may produce minor but definite changes in the ECG. (*2*) Acute myocardial infarction, which is sometimes hard to detect in a stuporous patient, may precipitate the acute acidotic episode. It is therefore wise to take an ECG of every patient whose diabetes is suddenly out of control.

ANXIETY NEUROSES

These may present baffling problems in differential diagnosis. There is no short cut to an accurate diagnosis. Each case requires painstaking study and evaluation Care must be taken not to induce iatrogenic disturbances during the diagnostic survey

MALINGERING

Special vigilance is needed, since drugs such as digitalis may have been used in order to modify the ECG Malingering is encountered mostly in connection with litigation.

ANEMIA

This may produce precordial pain, particularly in the presence of some degree of coronary narrowing. A routine diagnostic survey suffices to eliminate the condition from consideration

PRECORDIAL MIGRAINE

In a series of patients with migraine, 27 per cent complained of precordial pain which was an "equivalent" rather than an accompaniment of an attack of head pain [19] The pain is dull and heavy, and is usually located at the apex, but may occur elsewhere in the precordium or radiate to the left axilla or arm The patient suffers from a sensation of air hunger during the attack, and is unable to draw a satisfactory deep breath The pain is not induced by effort. Most of these patients are "heart conscious" Blood pressure, ECG, roentgenogram, and exercise tolerance are normal The migrainous character of this cardiac pain should be suspected if the patient is a young woman with a history of migraine.

CAFFEINE SENSITIVITY

Occasionally, the ingestion of coffee or tea may produce cardiac pain [37] The pain is apt to be of an aching character, and does not typically result from exertion This rare sensitivity is more likely to occur in patients with true coronary disease.

THYROID DISEASE

Both hyperthyroidism and hypothyroidism have been incriminated as a cause of anginal or precordial pain Zondek[64] listed the main cardiac signs of myxedema as cardiac dilatation, bradycardia, and hypotension Frequent electrocardiographic changes are (*1*) lowering of the P and T waves, (*2*) inversion of T waves, (*3*) prolongation of the P–R interval The hypothyroid type of angina responds quickly to thyroid therapy Routine diagnostic survey establishes the presence of hypothyroidism without difficulty.

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CHAPTER 14

Prognosis in Coronary Disease

EVALUATION OF the prognosis in coronary disease is subject to all the difficulties and errors of any statistical analysis, and especially of this condition. Sclerosis of the coronary vessels is so widespread that nothing can possibly be said today about the ultimate fate of the person who has some degree of sclerosis but no clinical complaints. It is indeed impossible to know who does or does not have atheroma, or to what degree, until there are clinical manifestations. The semantic problems of nomenclature constantly confront us. For example, let us take the simplest problem of all: Does the person with coronary sclerosis have coronary disease? If we regard sclerosis as a pathologic process rather than simply as part of the aging process, he certainly is suffering from coronary disease. Nevertheless, he is usually not classified as ill until he presents evidence of illness, that is, until the "person" becomes a "patient." This is probably a sensible attitude, since it acknowledges the fact that in the present state of our knowledge we are unable to tell what is going on within the arteries during early atheroma. On the other hand, it is plain that we are not taking into account persons with advanced sclerosis who do not present definite symptoms.

Uncritical acceptance of published figures would lead one to believe that the prognosis is much better than it once was. Possibly, it is somewhat better, thanks to modern therapy, but the most important factor in the apparent improvement is the ever increasing accuracy of diagnosis. Lesser degrees of infarction, now identifiable by better laboratory procedures, such as electrocardiography, have in recent years been put in the same category as the more severe cases, so that figures compiled in the past 20 years are not at all comparable with earlier ones.

With due appreciation of these hazards, let us consider the outlook for three categories of coronary disease: (1) coronary sclerosis without infarction (angina pectoris, etc.), (2) acute infarction, and (3) postinfarctive heart disease.

OUTLOOK FOR PATIENT WITHOUT INFARCTION

Any statement regarding the chances for healthy survival of a person with coronary sclerosis without signs or symptoms would be pure surmise; no accurate statistics are available. Probably, the chances are better than is popularly believed.

Some reasonably trustworthy statistics regarding angina pectoris are at hand. In one reported series, the average duration of life was 4.1 years, with a 50 per cent mortality in slightly more than 2 years;[~] these figures are somewhat unfavorably weighted, for all were hospital patients. In another series, half the patients were still alive at the end of 8 years.[26] In a third series, comprising 1700 cases, 679 were dead at the end of 4.7 years (for men) and 4.5 years (for women) after onset of symptoms.[45] Among the remaining patients, the longest survival was 35 years, with an average survival of 5.5 years. 32.8 per cent of the men were alive at the end of 5 years, and 34.5 per cent of the women; at the end of 10 years, the figures were 10 and 9.4 per cent, respectively, and at the end of 15 years, 3.5

and 1 per cent, respectively. The great John Hunter lived for 20 years after the onset of anginal pain, and many other long survivals are well known.

Any change for the worse in the electrocardiographic picture also changes the prognosis The presence of premature beats in the angina of effort is considered a grave portent,[39] whereas positive results in the anoxemia test bear no relation to the patient's chance of survival.[10] The presence of larger, "atherogenic" lipoprotein particles in the blood are believed to increase the tendency to infarction, and the prognosis is therefore less favorable in such patients.[25]

OUTLOOK FOR PATIENT WITH ACUTE INFARCTION

Two sets of factors are important in determining whether and how long the patient with an acute major infarction will survive (*1*) the state of the patient at the time of the attack, and (*2*) factors inherent in the attack itself

STATE AT TIME OF INFARCTION

COLLATERAL CIRCULATION The most important, immediate determining factor is the presence or absence of, a good collateral circulation The young patient with an acute process in one artery is likely to die suddenly because there has been no time for anastomoses to develop In general, a gradual coronary narrowing, which permits development of an adequate collateral flow, is of some advantage, but this is not the case if there is old infarction or a severe enough sclerosis so that scar tissue has replaced a considerable amount of normal myocardial tissue. Obviously, such a heart is closer to decompensation and has less cardiac reserve.

AGE Early death is much more likely if the patient is under the age of 40,[62] after the first 24 hours, however, the chances of survival improve sharply and the outlook is good. Between the ages of 40 and 60, the immediate [illegible] one series of 618 patients under the age of 60 the mortality rate was 28 8 per cent, while among 429 patients over the age of 60 the rate was 40 1 per cent.[41] The severity of the infarction and its complications are more important than the age of the patient in determining survival, although the infarction is usually more severe in older patients[60] In a series of 276 patients, the mortality in men rose steadily from 5 per cent for patients under age 44 to 35 per cent at ages over 65, in women, the rate was approximately 25 per cent at all ages, rising only slightly with advancing age.[37]

SEX The outlook for women is slightly worse than for men The main reason for this difference is that infarction occurs in women who are in an older age group than the men at the time of their attack. Other factors are that women are more likely to have diabetes or hypertension Among 572 patients with an average age of 61 5 years who suffered their first attack of infarction, the mortality rate was 21.8 per cent, the average age of the men in this series was 59 6, the mortality rate 18.6 per cent, for the women, it was 63 4 years, and 28.9 per cent.[43] In another series, the mortality rate for men was 31 per cent, for women 35 per cent[42] In a third series, the rates were 37 1 and 54 6 per cent, respectively[2] Women also seem to be more susceptible to cardiac rupture. Most observers agree that the prognosis for women is less good than for men.[34, 57]

PRESENCE OF HEART DISEASE Some observers have stated that a preexisting angina pectoris makes the prognosis more favorable,[14, 16 42] while others have maintained that it has no effect[5 46 52 60] Every one agrees that the presence of a previous infarction is disadvantageous in one hospital series, 36 4 per cent of the patients died during their first attack, of the patients with old infarction, 53 6 per cent died[5] Statistics gathered by Doscher and Poindexter[14] from the literature gave a mortality rate of 18.3 per cent for the first attack of infarction, and 30 per cent for second attacks; in their own series, the rates were 12 6 and 34 per cent, respectively. With few exceptions,[46 61] most observers believe that marked cardiac hypertrophy or coexisting

severe heart disease affect the prognosis adversely.

DIABETES This is universally conceded to be an unfavorable factor in prognosis

HYPERTENSION If present before the infarction, it is believed by some to have no effect on the immediate outlook except when accompanied by marked cardiac hypertrophy;[3, 16, 26] others, however, have reported that the mortality rate was 36 per cent in a group of patients with hypertension and 24 per cent in the group with normal blood pressure.[42] The latter opinion is shared by other investigators.[6] While this question has not been definitely settled, the effect, if any, of pre-existing hypertension is probably not great.[42] In one series, antecedent hypertension was reported to have had no effect on the prognosis up to 3 years after the acute attack; thereafter, the outlook was less favorable in this group.

OBESITY Opinion about the effect of overweight on the immediate prognosis is divided Some feel that the outlook for the obese patient is not as good,[16] while others have stated that obesity improves the prognosis[5, 6, 52] In one series, the mortality rate was reported as 32 per cent for the obese, 39 per cent for these of average weight, and 60 per cent for the underweight.[16] The combination of pre-existing angina and obesity enhances the patient's prospects for recovery, according to Block and associates[6]

FAMILY HISTORY OF HEART DISEASE The prognosis for a patient with a family history of heart disease is reported by some to be the same as for other patients But in my experience, the younger the patient, the more likely is there to be a family history of coronary disease and the more likely is death within 24 hours of an infarction

FEATURES OF INFARCTION AFFECTING SURVIVAL

Generally speaking, those clinical features of the illness which indicate a large area of infarction are also indicative of the patient's diminished chances for immediate survival

The character, location, radiation, and duration of the pain in myocardial infarction are thought by some to be of prognostic significance;[4, 44] others hold that the prognosis is not affected by any characteristic of cardiac pain during myocardial infarction.[33, 42] In my experience, pain which lasts beyond the fourth day is a definite sign of a poor prognosis The mortality rate in the rare "painless" infarctions is high,[5] probably because these patients do not seek medical advice early or take adequate rest.

Such features as high fever or marked leukocytosis should not be cause for despair in any individual case; neither should the absence of such signs lull one into a lack of caution

The immediate prognosis correlates directly with the degree of *leukocytosis*, the higher the leukocyte count, the worse the prognosis[2, 5, 42, 47] The mortality rate has been reported as 11 per cent for patients with a leukocyte count below 10,000, 28 per cent for those with a count between 15,000 and 20,000, and 38 per cent when the count was over 20,000[52] These figures are no doubt correct for large series, but I have seen several patients with leukocyte counts of over 30,000 who made good recoveries.

In the early stages of infarction, the prognosis is unrelated to the *sedimentation rate* When the rate continues high, progressive infarction should be suspected On the whole, I have found the sedimentation rate to be of little prognostic value.

Although it has been reported that the mortality rate correlates directly with the degree of *fever*,[5, 42, 47] many patients with high fever have recovered while some with little or no fever have fared badly. The temperature is often subnormal in shock. The death of 6 patients whose temperatures were subnormal throughout the course of their infarction has been reported.[5]

Heart failure of any sort is a grave prognostic sign.[33, 44] An ominous sign is the increase of venous pressure to over 200 mm.[47] About 50 per cent of the fatalities occur in patients with congestive failure[29] The mortality rate varies directly with the severity of pulmonary congestion, in one series, the rate was 10 per cent in patients without rales, but 68 per cent in those with severe pulmonary congestion.[42] Right ventricular failure is re-

portedly more unfavorable than left.[47] Decompensation, of course, is common in acute infarction. Among 108 patients with infarction, 10 had early, acute heart failure, decompensation developed in 41 who recovered from the acute phase of the infarction.[16] In another series of 110 cases, congestive failure was found in about 33 per cent.[39] The incidence of failure presumably is directly related to the size of the infarct, decompensation develops in 50 per cent of the patients with infarcts larger than 40 sq. cm., as compared to 32 per cent of the patients with smaller infarcts.[21] In a recent series, the mortality rate in 205 cases of acute infarction without failure was 10.3 per cent, in 73 cases with failure, the rate was 31.8 per cent.[17]

Generally, the more rapid the *heart rate* the higher is the mortality rate. A persisting rate of over 100 was found in 35 per cent of patients in one series, 76.3 per cent of the patients who died early had a fast heart rate, in contrast to 24.6 per cent with this sign in the group that recovered.[40]

The death rate in patients with gallop rhythm was 43 per cent, as compared to a mortality rate of 29 per cent in the group without gallop rhythm.[42] In another series, the mortality rate in the group with gallop rhythm was 53 per cent.[11] However, some investigators have stated that gallop rhythm does not affect the prognosis.[5]

Transient sinus tachycardia, ventricular premature contractions, or partial auriculoventricular block do not have an unfavorable effect on the prognosis. But persistent sinus tachycardia is a sinister prognostic sign, with a mortality rate of 57.1 per cent, when combined with heart failure, it is of even graver prognostic import.[33] Other arrhythmias, such as ventricular tachycardia, auricular flutter, or auricular fibrillation, which are signs of extensive infarction, have grave prognostic significance.[20] The mortality rate in one series of cases with posterior wall infarction was 12.2 per cent in those with normal rhythm and 30.8 per cent in patients with cardiac arrhythmias. In another series, all the patients in whom persistent auricular fibrillation or flutter appeared during infarction died,[1] of 22 such patients in my experience, 18 died within a week. The likelihood of death increases greatly with complete heart block.[13]

Opinion about the prognostic significance of *pericarditis* is divided, some have stated that it does not affect the prognosis,[5, 33] while others have found an increased mortality rate in the presence of pericarditis.[60]

Severe *hypotension* or *shock* make the prognosis much more serious (*see* Table 26, Chapter 15). The mortality rate in one series was 88 per cent for cases with shock, or more than double the rate of those without this complication.[15] In another series, shock was present eight times as often in the fatal cases as in the survivors.[61] In a third series of 57 hospitalized cases, 18 of the 26 who died were in shock on admission, and only 7 of the 31 who survived.[19] In patients with pre-existing hypertension, a drop in blood pressure to 100 or over apparently does not affect the prognosis if there is no shock.[5, 33] Some have found that a drop in pulse pressure below 25 mm. sharply diminishes the patient's chances of survival.[5, 12]

The prognosis is much worse for patients with *cyanosis*.[27, 42] *Dyspnea* and *rapid respiration* are unfavorable signs.[42] *Hiccups* are ominous, since most patients fail to survive a bout of them,[3] 8 of 10 patients whom I have seen with this complication died. *Anemia* and the blood *cholesterol level* are said to have no effect on prognosis.[5]

A pronounced rise in the blood *nonprotein nitrogen level* is considered an unfavorable prognostic sign. The rise is probably due to dehydration, oliguria, and other extrarenal factors. Azotemia is a regular accompaniment of shock.

Embolization causes a sharp increase in the mortality rate.

Patients with bizarre or atypical *electrocardiographic* features have a higher mortality rate higher than those with the usual patterns.[33, 49] Changing deflections which are not definitely related to healing, particularly after the first few days, are associated with a high mortality rate, almost always reflecting a complicated and progressing infarction. A spiked P wave over 2 mm. in height is likely to be accompanied by a tendency to arrhythmia and a higher death rate.[7]

Judging from the literature, anterior wall infarction is of graver prognostic import than posterior wall lesions;[2, 9, 11, 24, 26, 54] some observers, however, hold that the site of the

infarction has little influence on the outcome [8, 13, 22, 52] One report states that 57 per cent of posterior wall infarctions are "severe" because they tend to cause arrythmias and to change suddenly from slight to severe lesions.[35] The prognosis after 1 year is more favorable for cases with anteroseptal transmural infarcts than for patients with high anterior transmural ones, although congestive failure occurs with equal frequency in both groups [11] The long-term outlook for patients with lateral wall infarcts is somewhat better than it is for those with infarcts in other locations, especially septal.[22] Patients with auricular infarcts, on the other hand, have a definitely poor prognosis.[33]

Schnur[45] has assigned a numerical value to each of the clinical manifestations of acute infarction and has derived from them a "Pathologic Index Rating" which he feels to be of value in prognosis.

OVER-ALL IMMEDIATE MORTALITY RATE

Statistics regarding this are inexpressibly confusing The rate is variously given as between 3 1 and 51 5 per cent. The confusion with regard to nomenclature has been emphasized again and again in this book All degrees of infarction are lumped together in the literature. The diagnostic criteria differ from decade to decade Diagnosis is insecurely made on the basis of clinical data alone Since most studies are based on hospitalized patients, the selection fails to include those who are not ill enough or are too seriously ill to risk the trip to the hospital and those who die suddenly In any event, patients treated at home are omitted from almost all statistical studies There are some reliable reports from extremely competent specialists, but patients seen in consultative practice do not fairly represent the general population When two sets of observers report within a 3 year period (1949-1952) mortality rates of 3 1 and 51.5 per cent for a condition known as myocardial infarction, it should be plain that they are not selecting their patients in the same way.

For what they are worth, the following figures are selected from the literature. of 208 patients in their first attack, 33 per cent died within a month;[42] of 1247 patients with infarction, 51.5 per cent died during hospitalization at the Los Angeles County Hospital,[1] the immediate mortality in "coronary occlusion" is 50 per cent,[58] the death rate for hospitalized cases of uncomplicated cardiac infarctions is 34 per cent.[47] I am certain that these figures are too high; in 500 cases (398 men, 102 women) of first major myocardial infarction (typical electrocardiographic findings, typical clinical story, confirmatory laboratory findings) seen at the Kings County Hospital, the death rate within 1 month was 15 8 per cent

OUTLOOK FOR PATIENT AFTER INFARCTION

It is impossible to forecast the prospect accurately In one series of 488 cases, 75 per cent were alive at the end of 2 months, 50 per cent at the end of 1 year, 33 per cent at the end of 3 years, and 20 per cent at the end of 5 5 years [22] In another series, 52 per cent were alive and in good condition at the end of 2 years, 37 7 after 3 years, and 18 8 per cent after 6 years [83] In a third series, 66 per cent were alive 10 years after an acute attack, and 16 per cent after 20 years, 15 per cent were lost to follow-up [51] In a fourth series, of 420 patients who recovered from a coronary occlusion, nearly 80 per cent of those without hypertension survived at least 5 years, and 72 per cent of those with hypertension The 10 year survival rate was 57 and 33 per cent, respectively, the outlook for 5 year survival and seemed as good for those over the age of 50 as for the younger age groups [41] The most recent available report gives the results of a 10 year follow-up study of 211 patients who lived more than 2 months after a first infarction, a third of them lived for more than a decade. The outlook was found to be more favorable in the younger age groups and in those without heart failure or angina pectoris, three-fourths of the patients made a complete or partial economic recovery.[56] Peel[37] points out that the first 2 weeks are the dangerous period after acute infarction After that, the long-term prognosis is best for men between the ages of 50 and 54 years, the average life expectancy being 6 years The prognosis is somewhat worse in the younger age group,

and rises sharply at older ages. However, enough examples of extremely long survival are known to warrant guarded optimism in any one case. Table 25 shows the average life expectancy after myocardial infarction based on a series of over 1500 disability claims analyzed by the Mutual Life Insurance Company of New York.[23] Figure 97 illustrates the course and outlook for patients with acute major infarction in one recently reported series[8]

TABLE 25. LIFE EXPECTANCY AFTER MYOCARDIAL INFARCTION

Age at onset	Expectancy after infarction (yr.)	Normal expectancy (yr)
30 to 39	11 5	33 4
40 to 49	10 5	25 2
50 to 60	8 5	17.8

Most patients who survive are able to return to work, often with complete economic rehabilitation Of 42 patients who recovered, 18 returned to full duty in their previous occupations, 4 resumed 75 per cent of their earlier work, and 9 returned to 50 per cent, most of the occupations were sedentary, only 7 were unable or unwilling to resume any work, and 4 had retired from work before the infarction Of 100 of my patients who survived a first infarction, 41 returned to their earlier work at full time, only 21 could not, for physical or psychologic reasons, do any work In another series, 72 per cent returned to their former occupations,[8] and in a series of 361 patients in the younger age groups 50 per cent returned to full-time employment.[61] In still another series, 30 per cent of 354 patients returned to full work, and only 3 per cent were completely incapacitated.[42] The immediate mortality among 400 cases of acute infarction was 13 7 per cent;[32] in 100 cases treated with anticoagulants, the rate was 8.5 per cent. The survivors were divided into three groups· (*1*) Restored to their occupations with good prognosis, 37 per cent; 70 per cent of this group have survived for 7 years. (*2*) Limited occupation, with less favorable prognosis, 50 per cent. (*3*) Unfit to work, with poor prognosis, 13 per cent; only 29 per cent of this group survived for 2 years, and none for more than 3.

A recent analysis[31] of survival and rehabilitation after acute myocardial infarction showed that, of 500 patients who survived for at least 1 year, 415 were men, with an average age of 53.3 years at the time of occlusion. The survivors were divided into four groups on the basis of symptoms (Groups 1 to 4) and into another four groups on the basis of objective findings (Group A to D). Group 1 had no cardiac symptoms, and Group A had no detectable physical or laboratory abnormalities; Group 2 had mild angina or dyspnea, and Group B had mild cardiac enlargement or electrocardiographic changes, Group 3 had more severe angina or dyspnea, and Group C had marked electrocardiographic changes, and, frequently, aneurysm; Group 4 had intractable symptoms. Patients with definite congestive failure were put into Group 4

Of every 5 patients who survived for a year or more, 2 made a complete functional recovery, and 2 a satisfactory recovery with only mild exertional angina or dyspnea Of the patients who recovered, 75 per cent were working More than 50 per cent had lived over 5 years, and 1 out of every 5 for more than 10 years at the time of the survey Many patients with good functional recovery have enlarged hearts or electrocardiographic changes "Nevertheless," the investigators state, "when the physical examination, electrocardiogram, heart size and cardiac pulsation are normal, the patient has almost always made an excellent recovery and his outlook is good Another coronary occlusion may develop many years later in patients who have recovered completely, and they may again recover fully. The site of the infarction does not affect the prognosis after coronary occlusion The outlook is somewhat better in younger patients."

Cardiac symptoms, most commonly angina pectoris, persist in a large percentage of survivors. A fortunate few lose the angina from which they had suffered for varying lengths of

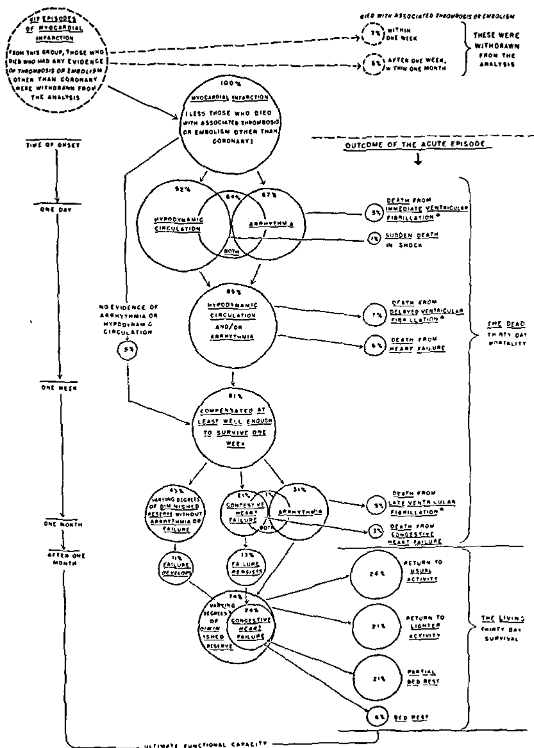


FIG 97. Proportion of patients with various clinical manifestations of hypodynamic circulation and arrhythmias at onset, at 1 day, 1 week, and 1 month following myocardial infarction, with the level of activity resumed by survivors (From Ball et al [9])

time before the infarction took place. Of 90 patients in the younger age groups, 30 suffered from postinfarctive angina,[17] in another series, 17 1 per cent had angina, and decompensation was present in 11 per cent,[53] among 400 survivors in a series collected from the U.S Army, 57 per cent recovered completely, pain recurred in 25 per cent, congestive failure developed in 2 per cent, pulmonary congestion in 4 per cent, and dyspnea without rales in 5 per cent [61] In another series, angina developed in 63 per cent, in some at once and in others years later, the angina more often followed anterior wall infarction than posterior wall infarcts, life expectancy was not affected by this symptom; 19 per cent of the patients ultimately had mild decompensation, and 9 per cent severe failure [42] A follow-up study of 202 patients showed that, regardless of blood pressure, angina developed in about 60 per cent, dyspnea, often the only cardiac symptoms, in over 50 per cent, and congestive failure in 25 per cent [29] The prognosis is not as good for patients who have some angina after infarction [33] The ECG in 77 per cent showed few changes toward normal after the acute phase was over, in 14 per cent there was a partial return and in 9 per cent a comp'ete return to normal, heart failure did not occur in the last two groups

The vital capacity was reduced in about 40 per cent of a series of cases of acute coronary occlusion, but returned to normal within 5 months in more than half of them, only 8 5 per cent of the patients remained with a sharply reduced vital capacity (less than 2000 cc)[37] In general, there is a close correlation between vital capacity and the degree of heart failure, *but not with the presence of pain. In* other words, a patient may have normal vital capacity, despite the presence of angina pectoris.

Exercise tolerance, as measured by the two-step test, was found to be below normal in two thirds of the patients who had had a myocardial infarction, and did not return to normal for 1 or 2 years after the infarction; it was usually good in patients who had made good recoveries from occlusion.[30]

Most observers believe that life expectancy after acute infarction is greater for young patients than for those over the age of 60;[24, 63] some, however, feel that age has no effect. The effect of sex on prognosis is less clear-cut than it is in acute infarction; the outlook is about the same for both sexes.[22, 42] The long-term outlook in anterior wall infarction is somewhat worse than in posterior wall infarction, according to some workers,[42, 59] while others do not believe that the site of the infarct has any bearing on the ultimate prognosis [22, 61] The presence of angina pectoris before infarction has been stated by some to be favorable,[8] by others unfavorable.[22] Antecedent hypertension affects survival little, if at all Survival of the acute attack is more difficult for the patient with diabetes, but the long-term mortality rate is only slightly higher [22] There is general agreement that survival is directly related to the severity of the infarction A ventricular aneurysm does not of itself change the outlook.

The likelihood that a patient with an infarction will die from a cardiac condition is overwhelming In a follow-up of 80 patients, 28 died suddenly, 32 died of known infarction, 16 of congestive heart failure, and only 4 of causes not related to the heart.[42] In another series of 52 cases, 34 died with new infarctions, 10 with heart failure, and 3 with pulmonary emboli [22]

From a consideration of all the factors mentioned in the last few paragraphs, the physician may feel that he can at least broadly assess his patient's chances for long life. However, the course of coronary disease is notoriously uncertain and we seek constantly for new ways to evaluate our patients' outlook The ECG gives us little help but there is much reason to believe that the BCG may be more useful In 100 patients who survived a first *infarction, the BCG reverted to Grade 2 or* better in 65, of these, 55 returned to a useful occupation and only 1 died, in 35 with advanced abnormalities, only 5 died [25] In 50 patients with Grade 2 changes or better after a first attack whom I have followed for 3 years, only 1 has died of a subsequent infarction, and heart failure has developed in 1 patient only.

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CHAPTER 15

Treatment of Acute Infarction

WHILE THE treatment of acute major myocardial infarction must vary with the needs of the individual patient, some basic principles may be set down here. The management of minor infarction varies even more, but the physician who has attained skill in the treatment of the more seriously ill patient will have little difficulty.

MANAGEMENT OF FIRST TWO DAYS

As soon as the diagnosis of myocardial infarction is made, the following steps, in the order given here, should be taken unless the exigencies of the case make a change necessary.

1 Bed Rest. Put the patient to strict bed rest for at least 24 hours; this applies to *all* patients.

2 Relief of Pain. Give immediately ¼ grain morphine sulfate and 1/100 grain *atropine sulfate, subcutaneously, if necessary*; this may be repeated several times at one-half hour intervals. If the pain is extremely severe, ½ grain morphine may be administered intravenously at once. I do not hesitate to use this route when it seems necessary. Other measures may be taken if vomiting occurs, but this should not be invariably attributed to the morphine, since it is a common occurrence *in infarction*.

Substitutes for morphine may be used. Any one of the following may be administered by mouth or subcutaneously instead of ¼ grain morphine: Demerol (Pethedine) is the most useful and the most widely employed, in a dose of 75 to 100 mg.; methadone, 15 mg; Dilaudid, 1/32 grain; Pantapon, ⅓ grain. Paraldehyde is another substitute; it is usually effective by mouth, but 5 to 8 cc. may be given intramuscularly, or smaller amounts intravenously. Oxygen sometimes has analgesic results. In intractable pain, 0.48 Gm aminophylline or 0.03 to 0.09 Gm papaverine hydrochloride may be administered *very slowly* by vein.[13] I have not found it necessary to use either of these recently.

For mild pain, ¼ to ½ grain codeine may suffice. An ounce of whisky sometimes gives relief.[81]

3 Oxygen. This should be on hand in every case. It may be administered from the beginning to all patients, and it should never be withheld if there is severe pain, cyanosis, or dyspnea. The usefulness of oxygen in infarction has been demonstrated in cases with (*a*) cyanosis, (*b*) shock, (*c*) severe and persistent cardiac pain, (*d*) dyspnea, (*e*) acute pulmonary edema, (*f*) congestive failure, (*g*) certain cardiac arrhythmias, (*h*) rising heart rate, (*i*) sharp fall in blood pressure, (*j*) marked leukocytosis, (*k*) high fevers, (*l*) Cheyne-Stokes respiration.[49]

In practice, it is not necessary to wait for any of these signs (all of which are associated with major infarction). I often order oxygen when the diagnosis of infarction is clearly established. When the cost might be burdensome, or the patient is likely to be too apprehensive about oxygen therapy, the decision must be made on the basis of one's own clinical experience and judgment.

In most cases, the tent is the most satisfactory method of oxygen administration. The modern tent is transparent and the operation quiet; in unpleasantly hot weather, it also provides a comfortably air-conditioned atmosphere. However, its cost may be prohibitive, and patients with even mild claustrophobia prefer other methods. An oxygen concentration of 45 to 50 per cent suffices in most instances of infarction. The mask is useful when

a tent is not available or cannot be used for other reasons, or when relatively high oxygen concentrations are needed, 70 per cent concentration can be maintained indefinitely without toxic effects Pure oxygen may be used, but only for short periods, since it may cause pulmonary irritation. The nasal catheter technic, with proper care, is satisfactory; at 8 liters per minute, a concentration of 42 per cent can be attained.

4 Management of Family. A responsible member of the family should be told the diagnosis A guarded prognosis is given, and *the probable duration of bed or bedside rest* is stated at once so that suitable arrangements can be made. Visitors, except for immediate *members of the family, are not permitted* The patient should be reassured, but lengthy discussions are inadvisable at this time. Such words as "coronary" or "angina" should be avoided except when they are necessary to convince the patient that he must remain in bed.

5. Hospitalization. This question should be discussed at once A patient who is in shock or gravely ill should not be moved If the patient's condition permits, removal to a hospital, if decided upon, should be done as soon as possible. Such a move is usually advisable if satisfactory hospital facilities within the patient's means are available

6. Nursing Care Satisfactory nursing should be available throughout the day and night Whenever possible, a stranger, preferably a sensible and amiable trained nurse, should take over

7. Diet For the first 24 hours, the patient should be given gelatin desserts, toast, cereal, and fruit juices, iced drinks should be avoided Small amounts of ginger ale or cracked ice may be given if there is much nausea

8. Bowel Care. Bathroom privileges should be denied The patient should use the bedpan, in exceptional cases, he may be permitted to sit up in bed on the bedpan or a commode placed next to the bed may be used Bowel movement may be neglected for the first 2 or 3 days Thereafter a small enema may be given every other day for 2 weeks, this is less likely to cause strain than the use of laxatives Otherwise, milk of magnesia, a teaspoonful after each meal or 1 to 2 tablespoonfuls at night, may be administered The patient often has his own preference for a laxative agent, some do well with glycerine suppositories

9. Sedation While the opiates are being used, the patient is usually quiet Once he is free of pain, however, he often becomes restless and apprehensive, some sedative should then be administered During the first 2 days, I prefer ½ grain (30 mg) phenobarbital four times a day, other sedatives may be substituted. After 48 hours, the drowsiness which this dose of phenobarbital sometimes induces may become troublesome, and *the dose should be reduced to ¼ grain At night,* it is usually wise to use a hypnotic, 3 grains (0 2 Gm) sodium amytal or 0 05 Gm chloral hydrate are effective except in the extremely restless patient, for such patients paraldehyde, or a barbiturate intramuscularly, is indicated.

10 Laboratory Procedures (*a*) An electrocardiogram should be taken as soon as possible. If it does not yield diagnostic data, another should be done daily or 2 or 3 days later If repeated electrocardiography is not feasible, for economic or other reasons, the first ECG may be delayed for 3 days, provided the diagnosis seems certain otherwise (*b*) Urinalysis should be done on the first day (*c*) *If anticoagulant therapy is planned, the* prothrombin time should be determined, Dicumarol should never be used until this is done (*d*) The sedimentation rate or serum transaminase level should be determined on the first day for use as a control (*e*) All other diagnostic procedures may be deferred

Antibiotics need not be given in acute infarction unless there are specific indications for doing so Fever early in the course is not usually a sign of infection

MANAGEMENT AFTER FIRST TWO DAYS

REST

There is no question about the management of the patient in shock he should be in bed There is little question about the patient with minor infarction his treatment may be liberalized at once and he may be permitted to get out of bed after the first day or two But opinion about the amount and kind

of rest required by the patients with major infarction—the vast majority of them—is considerably divided. No one today insists that the patient with an uncomplicated infarction remain flat in bed, hardly moving a muscle, for 6 weeks, a common practice 10 years ago. Work with rats led some investigators[76] to express the opinion in 1944 that prolonged restriction of activity after cardiac injury might actually be harmful, and to advise shortening the period of bed rest to 2 or 3 weeks The consensus of the many cardiologists with whom I have discussed this is that a patient should be kept at bed rest, with fairly free motion, for 2 to 3 weeks, thereafter, chair rest for another 3 weeks, with gradually increasing ambulation, so that after 6 weeks the patient is walking freely about the room and using the lavatory if it is close by

ARMCHAIR TREATMENT Ever since 1944, when William Dock[24] started to use immediate chair rest and the commode in the treatment of his patients, a re-evaluation of the theory of bed rest has been taking place, and the ideas advanced by Dr Samuel Levine of Boston have become increasingly popular He and his co-workers[47] have shown that flat bed rest permits maximal venous return from the periphery, with an associated increase in blood volume, venous pressure, and ventricular diastolic filling, thus augmenting the work of the heart. Sitting up permits gravity to mobilize fluid into dependent parts of the body rather than into the pulmonary circuit, and the vital capacity may be increased by as much as 200 cc According to Levine and associates, bed rest "saps morale, provokes desperation, unleashes anxiety and ushers in hopelessness." It fosters constipation, thrombophlebitis, osteoporosis, negative nitrogen balance, hypostatic pneumonia, atelectasis, and prostatic difficulties Pulmonary edema may actually be prevented by an enhanced sense of well-being, indicating that emotion may sharply increase the cardiac output.[47] The over-all mortality among their patients was 9 per cent, and they encountered no complications which could be attributed to the treatment.

A detailed study of 6 patients[19] has shown that when the patient assumes the armchair position after being recumbent the heart rate usually increases slightly and the mean circulation time is lengthened In 4 of the 6 patients, the calculated pulmonary blood volume was diminished, in 1 of them by as much as 685 cc., with prompt relief of dyspnea. The hematocrit value increased slightly, and the stroke volume decreased The work of the heart was reduced by 23 per cent when the patient was in the armchair position On the basis of the evidence in this study, it seems possible that the coronary flow is not diminished and that it may even be increased so long as there is no postural hypotension.

Levine's patients are permitted, except when they are in shock, to get into an armchair 24 to 48 hours after onset of the infarction, and to stay there to the point of fatigue, usually several hours the first day. "With a comfortable chair close to the bedside, the patient is helped to sit up in bed by 2 people, one on either side His legs are then dangled over the edge of the bed He stands, with support on both sides, and is guided and helped into the chair. Care is taken that no pressure is exerted by the chair on the popliteal spaces or calves in order to avoid interference with circulation." A bedside commode is used The patient is soon allowed to feed himself and to comb his hair, but not to shave himself. This does *not* mean early ambulation, Levine emphasizes The patient should rest for 4 to 6 weeks, at the end of which time scar formation should be complete or well on its way. Others are favorable in their reports of this regimen, although some[52] wait until the fifth day, on the average, before allowing the patient to sit up A low bed rather than a hospital bed should be used

A modification of the Levine method has been used in 39 patients by Beckwith and associates,[5] their report on the results is enthusiastic Armchair treatment was started only after shock had been controlled or pain had almost disappeared The schedule followed was: 30 minutes three times a day for 3 days, 60 minutes three times a day for 3 days; 90 minutes three times a day for 6 days, thereafter the patient was allowed up at will This regimen seemed to be attended by psychologic and physical benefits; no apparent ill effects were suffered by any of the patients. In their opinion, the risk of aneurysm formation is probably not increased in patients treated

by the armchair method and might even be lessened since the cardiac work is reduced, this is in contrast to the belief that the risk is increased in patients who do not have adequate bed rest.[63] They, too, emphasize that chair treatment does not mean early ambulation

I have found the armchair regimen useful in over half of my recent cases of infarction, but the patient, and often his physician, must be re-educated Only an intelligent and cooperative patient takes the physician at his word that chair rest does not mean ambulation The treatment may encourage an easygoing attitude toward the gravity of the condition, which may cause trouble when the patient who is being treated at home is inadequately supervised I have been asked to see patients who inferred from the family physician's instructions that a strenuous social life as well as sexual activity were permitted There is considerable risk, too, that laymen in close association with the patient may feel that "he isn't sick if he's not in bed", even the hospital staff may share this view[53] Surgical beds are becoming available which permit dropping the legs as well as raising the head. If such a bed can be obtained, the patient need not be lifted out to assume the armchair position

The use of 9 inch wooden blocks under the headposts of the bed has been suggested,[62] to prevent nocturnal gravitation of fluid and possible paroxysmal dyspnea. A board or box at the foot of the bed will keep the patient from sliding forward

LENGTH OF REST Whether the armchair regimen has been used or not, the patient with uncomplicated major infarction is out of bed by the beginning of the fourth week Getting the patient out is usually preceded by "dangling" (sitting on the edge of the bed with a support under the feet) for a day or two

There is general agreement that even in favorable cases, rest should be continued for 6 weeks, by which time scar formation is firmly established and full mobilization may be permitted. The patient may be allowed to take a few steps to a comfortable chair near the bed or to a nearby lavatory during the second 3 weeks He may be permitted to stand to urinate, but a bedside commode or bedpan on the chair should be used for bowel movements.

Under certain circumstances, bed rest, or at least very strict armchair rest, is essential during the second 3 weeks These circumstances are (*1*) If the sedimentation rate, leukocyte count, or temperature remains unaccountably high (*2*) If there is tachycardia or decompensation (*3*) If changes in the electrocardiogram continue to appear (*4*) If cardiac pain returns after having subsided

Starting with the seventh week, the patient may be allowed to walk around in his home, or in the hospital, even when the sedimentation rate is high or there is mild tachycardia on exertion Complete rest should be continued if there is tachycardia at rest, or decompensation Every effort should be made to re-establish compensation, but here the rules for treating cardiac decompensation in other conditions begin to apply Intractable mild dyspnea, or edema of the legs, or an enlarged liver may still be compatible with some mobilization Naturally, the over-all prognosis is somewhat worse, and the period for complete rehabilitation, especially economic, will be prolonged

Continuing change in the electrocardiogram, except when this is definitely recognized as due to healing of the infarct, is an absolute indication for continued rest Even minor changes, especially in leads not previously affected, should be regarded as indicative of progressive myocardial damage I have found the outlook for complete recovery in such patients much worse Insistence on a stable electrocardiogram before allowing full activity is a wise precaution two electrocardiograms, a week apart, should be identical

NURSING CARE AND GENERAL MANAGEMENT

Quiet and relaxed nursing by someone outside the family, preferably a professional nurse, is advisable for the first few days The length of this period is best left to the judgment of the physician, it will depend, among other factors, on the economic status of the family and the patient's and the family's attitude to the illness Usually, the time ahead will be difficult financially, and it is unwise to insist on expensive nursing care which is unnecessary if there are capable and willing relatives to help.

LEG AND ARM EXERCISES These should be started early in the illness. Leg exercises will help avoid phlebothrombosis Simple bending of the knee and rotation of the foot at the ankle for a few minutes at a time, but on a definite schedule several times a day, suffice Elastic bandages may be applied below the knee from the first day The upper extremities, especially the left, should be put through a full range of motion three or four times a day, this may help to prevent painful stiff shoulders or the shoulder-hand syndrome later on

DIET A light diet, with frequent, small meals, should be given Many clinicians use an almost fat-free diet In any case, a low salt diet is advisable, in view of the threat of decompensation Master's[71] insistence on a low-calorie diet is probably correct

BATHING A bed bath may be given for 5 weeks A tub bath after the fourteenth day, as some advise,[52] involving as it does at least two lifts, seems inadvisable except when bed bathing unduly distresses the patient

TREATMENT OF HICCUPS

This sinister complication sometimes responds to morphine or barbiturate sedation Carbon dioxide inhalations are not suitable for patients with acute coronary disease Quinidine, contrary to early expectations, is without value Chlorpromazine (Thorazine), 50 mg intravenously, is probably the best drug for intractable hiccups, the dose may be repeated after 2 to 4 hours, if necessary[34] If the patient is debilitated or acutely ill, 25 mg may be given intravenously and the other 25 mg intramuscularly. After the initial dose, 25 mg may be given by mouth three times a day Bilateral phrenic nerve crush was reported to be successful in 2 of 5 patients with intractable hiccups complicating myocardial infarction[74] I have seen 1 case successfully treated by phrenic nerve crush after all other measures had failed, but this measure is not recommended except in a desperate situation.

PSYCHOLOGIC REHABILITATION

Some time during the first month of illness, the question of the patient's psychologic rehabilitation must be faced squarely. Dunlop[8] says:

> An attitude of unrelieved gloom on the part of the attending physician is not only inhuman but is not justifiable in view of the fact that 2 out of every 3 cases recover who survive long enough to be seen by a doctor. The risks to be run during convalescence must be kept in mind by the doctor, but must not be used as a bogey to frighten the patient into submission And it should be realized that not the least of the patient's risks is, that of developing an eventual cardiac neurosis which may be much more crippling than his true organic lesion.

Soon after the patient stops worrying about his pain and the possibility of imminent death, he begins to think about his future. Coronary disease usually affects heads of households, persons who have often led aggressive and successful business lives. Depression, anxiety, and fear of permanent invalidism make their appearance early. Obviously, the physician must be reassuring and optimistic. Within the bounds of common sense, he should try to communicate this feeling to members of the family. Discussion of the patient's earning capacity should be deferred for a time, but sooner or later the doctor must discuss this with the persons most concerned. He may honestly say that the chances of long survival are excellent; he may also safely say that at least two thirds of the patients return to a gainful occupation, and that about half return to their former work without restriction. He should point out that except for those who do heavy manual labor, patients usually are able to earn their living within 2 months after activity is resumed Some restriction may be necessary if the patient's former occupation was physically or mentally arduous. Lawyers, for example, would do well to give up fatiguing trial work Angina pectoris or heart failure may compel some modification of this program, but this need not be discussed with the invalid until the appropriate time The patient will need reassurance about future sexual activity, after the first 2 or 3 months, when it is interdicted, most patients are able to resume a satisfactory sexual life.

TREATMENT OF HEART FAILURE

In a sense, heart failure is present in every instance of major myocardial infarction. The heart no longer operates efficiently and a host of changes impair the normal circulation

of the blood How this differs from the cardiac failure so often seen in other forms of heart disease is primarily of interest to the physiologist; the clinician need only recognize congestive heart failure when it occurs and be prepared to treat it. Of the two, diagnosis may be the more difficult.

Several basic rules may be of assistance. Tachycardia and hypotension, in the absence of other signs, do not necessarily indicate heart failure. The signs of the type of heart failure which requires conventional treatment are: rales, edema, liver enlargement, etc. In general, treatment should be about the same as if infarction were not present, although a few modifications may be necessary. Whether cardiac decompensation occurs soon after a major infarction, or later in life, it responds satisfactorily to proper treatment There is no reason to believe, as has been claimed by one observer,[27] that decompensation is more difficult to manage than other forms of congestive failure.

DIGITALIS

Clinicians have long feared to use digitalis for patients with heart failure after infarction, *but the fear* is not borne out by the good results obtained when digitalis is properly used in patients with infarction.

Digitalis supposedly increases cardiac irritability (and the likelihood of ectopic rhythm). There can be little doubt that ventricular tachycardia occurs more commonly in the patient receiving digitalis, and it has been reported that an increased susceptibility to digitalis develops some days after acute infarction[77] Increased coagulability of the blood has also been reported to result from digitalis[51a, 60] Bedside experience, however, has served to quiet these misgivings. A study of 100 patients, 50 receiving digitalis and 50 controls, showed that ectopic rhythms did not develop in any of the 50 patients given digitalis[2] Others, too, have used digitalis without untoward incident[14, 75] I have used digitalis to treat infarction for many years, and have had only good results with proper use It is generally agreed that digitalis should be administered with caution and that full digitalization should be slower than in other situations. The best digitalis drug to use is the one with which the physician is most familiar.

In patients with coronary disease, digitalis, it has been reported, often increases anginal pain It has also been reported that, in patients with angina, digitalis lowers the threshold to discomfort on exertion, and causes earlier changes in the electrocardiogram both on exertion and at rest.[33, 49] Possibly, alterations in cardiac output in such cases may be the cause of a relative coronary insufficiency and clinical discomfort, even without an absolute decrease in coronary flow[25] On the other hand, some investigators found that digitalis did not increase the danger of cardiac rupture nor did it increase pain or lessen the capacity for work in persons with coronary disease

In animals, digitalis seems to reduce the coronary blood flow[22] The action may be inconstant, but digitalis derivatives (*e g*, Digifolin, ouabain, strophanthin), even in therapeutic doses, have sometimes had a direct constrictive action on the coronary arteries[50] In revived, perfused hearts, digitalis reduced the coronary flow in normal hearts but augmented the flow in dilated hearts,[44] this effect parallels the action of the drug on the diastolic volume of the heart A decreased coronary sinus outflow was found both in heart-lung preparations and in the intact *animals for 10 minutes after the use of* digitalis, followed by a persistent increase in flow, it was concluded that the effect was not pronounced enough to contraindicate its use in patients, except in cases of marked coronary insufficiency[37] Strophanthin caused a moderate initial decrease in coronary sinus flow in dogs, followed by a definite and sustained increase, there were no changes in blood pressure or heart rate[70] Strophanthin increased coronary flow[53] when administered to anesthetized dogs in whom coronary insufficiency had been produced by pituitrin, chloroform, or ligation of the left ascending artery.

At the Mayo Clinic, the coronary flow in trained dogs was carefully measured by means of the thermostromuhr.[22, 32] Intravenous injection of 30 per cent of the calculated minimum lethal dose of digitalis had no effect on the coronary flow, toxic doses, however, definitely reduced the coronary flow for hours to days This reduction could not be explained on the basis of changes in pulse rate or systemic blood pressure.

In cats with partially healed myocardial infarction, ectopic ventricular rhythm of death was produced with 25 per cent less digitalis

than in cats with normal hearts.[77] Presumably, the healthy muscle immediately surrounding the infarcted area is especially irritable and digitalis sets up abnormal impulses leading to ventricular tachycardia or fibrillation. The investigators concluded that a 25 per cent reduction in dosage would provide an adequate safety factor

Although experimental evidence would seem to indicate that digitalis may have an adverse effect, one must be wary in transferring the results of animal studies to clinical problems in man Dogs seem to be less sensitive than man to digitalis, and it is difficult to estimate digitalis dosages in dogs which would be equivalent to those used in man It is also possible that diseased coronary arteries may react differently to digitalis, just as older cats are somewhat more sensitive to the drug than younger ones Nevertheless, it must not be overlooked that strong ventricular systoles may strain the heart or dislodge mural thrombi, although the danger of these effects seems slighter than the danger from vasoconstriction or the setting up of ectopic rhythms Wegria,[40] in his review of the pharmacology of digitalis, concludes

> It seems that in the unanesthetized dog therapeutic doses of digitalis, digitalis bodies and digitalis-like drugs do not modify the coronary flow very much, if at all Large doses may decrease the coronary flow The studies made in acute experiments on anesthetized animals have yielded conflicting data, as have studies made on the heart-lung preparation or similar preparations

DIGITALIS LEAF This is a cheap and effective form of the drug It is dispensed in ablets of 0 1 Gm (1½ grain or 1 U S P unit), 12 to 30 units are needed to digitalize the average adult For a man of 150 pounds, 1.5 Gm (22½ grains or 15 U.S P. units) would be used, 1 unit for each 10 pounds over or under this weight being added or substracted The initial dose is half the digitalizing dose—8 tablets to start, then 3 or 4 tablets every 4 to 8 hours until complete digitalization is reached often 16 to 48 hours. The daily maintenance dose is usually 1 tablet.

DIGOXIN This drug, a derivative of lanatoside-C, is the one I have been using most often. For rapid digitalization, 1.5 mg (6 tablets) should be given at once. An effect is noted within 2 hours and becomes maximal at 6 hours, thereafter, 1 or 2 tablets may be given at 6 hour intervals, if required. The maintenance dose is 1 to 2 tablets a day.

GITALIN (GITALIGEN) This is a satisfactory product, with a fairly wide margin of safety It is marketed in 0.5 mg tablets. Digitalization can be attained rapidly with an initial dose of 5 tablets (2.5 mg.), followed by 2 tablets (1 mg) every 6 hours until therapeutic effect or toxicity is noted. The average digitalizing dose is 12 tablets (6 mg) Most patients can be maintained on 1 tablet a day. I have found this preparation effective and of low toxicity.

DESLANOSIDE—U.S P. XV (CEDILANID D) This drug is marketed in ampules containing 2 or 4 ml, each milliliter representing 0 2 mg The usual digitalizing dose is 1 6 mg, but this should not be given all at once in the presence of acute infarction. In the acute failure of infarction, or when there is a rapid ventricular rate resulting from auricular fibrillation or flutter, 0.8 mg. (4 ml) should be given by vein at once, followed by 0 2 to 0 4 mg. every 2 hours until 1.6 mg. have been given or a full therapeutic response is achieved.

STROPHANTHIN This is the most satisfactory preparation for emergency use Ouabain, a pure glycoside derived from *strophanthin G, is the drug which I use,* as a rule Strophanthin K is also available. An initial dose of 0 25 mg. should be given by vein, followed by 0.1 mg. every hour until there is full therapeutic effect (usually within 2 hours) or signs of toxicity. No more than 1 mg. should be given in 24 hours. Most of the effect disappears within 2 days, so that administration must be repeated daily, or, preferably, a digitalis drug by mouth should be substituted

MANAGEMENT OF ACUTE FAILURE

The following are the steps to be taken: (*1*) Oxygen at once. (*2*) Sedation and relief of pain. (*3*) Treatment of shock, if present. (*4*) Digitalis or similar glycosides (*5*) Mercu-

hydrin or an equivalent mercurial diuretic, intramuscularly (never intravenously); indications for use are the same as in other instances of heart failure. The usual dose is 2 cc, but it may be wise to use 1 cc. as an initial dose. In shock, venous blood flow is so poor that good diuresis seldom results; it is therefore better to wait until there is some diminution of shock. Mercuhydrin may induce urinary retention in elderly men with large prostates who receive morphine at the same time.[31] (6) Other measures, such as salt restriction, should be used, as in other types of heart failure.

TREATMENT OF PULMONARY EDEMA

The tendency to pulmonary edema may be decreased by the armchair treatment and by raising the head of the bed. Nevertheless, it remains a serious complication, a terrifying one both for the patient and the observer. Treatment comprises:

1. Sedation. Immediate administration of ¼ grain morphine and 1/100 grain atropine, subcutaneously; this may be repeated early and often. Fear and anxiety may precipitate, and will certainly help to continue, an attack of pulmonary edema.

2. Venesection. Unless there are contraindications, 500 cc. of blood should be withdrawn rapidly. This may be done without fear.

3. Oxygen Therapy. Oxygen in high concentration should be used promptly. Antifoaming agents are becoming popular. An alcohol-oxygen vapor may be used, administered by nasal catheter, with 95 per cent alcohol to patients who are conscious, and by mask with 30 to 40 per cent alcohol if the patient is unconscious.[39] The oxygen is permitted to bubble through the alcohol.

4. Tourniquets. These may be used on all the extremities in addition to, or instead of, venesection.[44] Inflated blood pressure cuffs make satisfactory tourniquets. Such "bloodless phlebotomy" is sometimes useful in an emergency. Treatment should be terminated very slowly, so that the myocardium is not subjected to a suddenly increased blood volume.

5. Digitalis Therapy. Digitalis and similar glycosides are often necessary at this point.

6. Mercurials. A mercurial diuretic to rid the body of excess fluid (e.g., 1 to 2 cc. mercuhydrin) is usually in order. It should be given as the patient is beginning to recover.

TREATMENT OF SHOCK

In view of the fact that shock usually occurs in major myocardial infarction, in which the heart's ability to function as a pump may be impaired beyond remedy, the results of treatment have been discouraging. Recently it has seemed justified to assume a somewhat more optimistic attitude. It seems possible that in many cases the blood pressure can be raised, at least temporarily, and the mortality rate somewhat reduced. Prompt diagnosis and early treatment are essential.

Application of elastic bandages up to the midthigh and raising the foot of the bed may be the first measures. The latter may not be feasible because of the presence of congestive failure and the patient's undue apprehension when in this position.[33] Digitalization is indicated when congestive failure is present. If the blood pressure is unobtainable, immediate blood or plasma transfusion may be instituted, followed by the other measures to be given.

SYMPATHOMIMETIC DRUGS

These include Norepinephrine, epinephrine, phenylephrine, paredrine, mephentermine, ephedrine, aramine, isopropylarterenol, methoxamine.

NOREPINEPHRINE (NORADRENALINE, ARTERENOL, LEVARTERENOL, LEVOPHED). Norepinephrine has so far received the most attention and seems the most promising. It is obtainable in 4 mg. ampules (Levophed), which must be diluted with 1000 cc. of distilled water or 5 per cent dextrose in water. Saline solution should not be used. In exceptional cases, the concentration may be increased from 4 to as high as 16 mg. per 1000 cc.

If the veins are collapsed, venesection may be necessary for administering the drug. A polyethylene catheter should be employed; a needle of large bore may be used if a catheter cannot be obtained. The rate of flow should be adjusted so as to bring the systolic pressure up to 100 mm. Hg, or to 110 to 125 mm.

Hg in previously hypertensive patients.[66] The flow should be started at 15 drops per minute and increased by 5 drops per minute every 3 minutes until the desired effect is obtained. It may be imperative to increase the rate of flow rapidly if the patient is critically ill If the pressor response is inadequate, or if it can be maintained only with a rate exceeding 40 drops per minute, a higher concentration of the drug (up to 16 cc. of 0.2 per cent solution per liter) should be administered from a second flask connected to the other arm of a Y tube [60] The blood pressure should be read every few minutes

The amount of drug is gradually reduced after the blood pressure has been sustained for several hours, sudden withdrawal might cause a drastic drop in blood pressure. Intravenous infusion of 5 per cent dextrose in water should be continued for 24 hours or more thereafter, this will prevent loss of time in resuming medication, should the blood pressure start to fall again.

When the standard administration of norepinephrine fails to restore the blood pressure, the following may be tried (*1*) increasing the rate of flow, (*2*) increasing the drug concentration, (*3*) infusing 250 cc or more of plasma through another vein,[13] (*4*) administering cortisone aldehyde, which may enhance the action of the norepinephrine,[11] (*5*) administering cholinesterase, which has been reported to restore lost responses to the sympathomimetic drugs,[41] and (*6*) intra-arterial blood transfusion [11]

Norepinephrine stimulates the myocardium directly [62] In swine, it dilates the coronary arteries about two and a half times as much as does epinephrine; it dilates coronary arteries which have a certain degree of tone, but in fully dilated specimens it produces an insignificant degree of vasoconstriction.[12] In experimental myocardial ischemia, small doses of the drug result in a striking rise in oxygen tension [67] There is no evidence of increased cardiac irritability or of subjective reactions, and there are no apparent ill-effects in digitalis-treated patients.[54]

The results of norepinepthrine treatment, as collected from the literature by Binder and associates,[11] are listed in Table 26. Using rigid criteria for the diagnosis of shock, they treated 25 patients and obtained a significant reduction in the mortality rate. The time of onset of shock, the duration of therapy, and the total dose of norepinephrine did not affect survival, but the amount of drug required per unit of time was significant, the outlook for those needing more than 1 mg per hour being worse. The blood pressure at the beginning of treatment was of no prognostic significance, patients with an imperceptible pulse responded as well as those with pressures of 40 to 80 mg Hg

The hazards of treatment are commonly venospasm and phlebitis, especially if there is leakage. Hot packs at or just above the point of injection may help to prevent these complications [13] In patients with diabetes or peripheral vascular disease, the leg veins

TABLE 26 RESULTS OF NOREPINEPHRINE THERAPY OF CORONARY SHOCK AS REPORTED IN THE LITERATURE[11]

Source and year	*No cases reported*	*Pressor effect*		*Relief of of shock*		*Survival*		*Mortality*	
		No.	*%*	*No*	*%*	*No*	*%*	*No*	*%*
Smith and Guz (1953)	6	6	100	4	67	4	67	2	33
Livesay and Chapman (1953)	6	5	83	1	17	1	17	5	83
Miller and Baker (1952)	7	4	57	1	14	1	14	6	86
Gazes *et al.* (1953)	7	7	100	7	100	6	86	1	14
Miller *et al* (1953)	9	8	88	5	56	5	56	4	44
Calenda *et al* (1953)	13	9	70	4	31	2	15	11	85
Kurland and Malach (1952)	14	10	71	9	64	4	29	10	71
Moyer *et al.* (1953)	14	12	85	6	42	6	42	8	58
Sampson and Zipser (1954)	30	27	90	20	67	16	53	14	47
Totals	*106*	*88*	*83*	*75*	*54*	*45*	*42*	*61*	*58*

should not be used for infusion. In rare cases, pulmonary edema may occur.[16] Use of large quantities of fluid should of course be avoided in a patient with pulmonary congestion, but whether this condition is an absolute contraindication is still uncertain. I prefer the intermittent administration of Mephentermine sulfate in such cases

EPINEPHRINE While this is a mild coronary vasodilator,[50] it cannot be advised as a satisfactory drug in coronary disease. It decreases cardiac efficiency and increases cardiac work and metabolism more than it does the coronary flow.

PHENYLEPHRINE HYDROCHLORIDE (NEO-SYNEPHRINE HYDROCHLORIDE, META-SYNEPHRINE HYDROCHLORIDE) This drug is given in doses of 5 mg intramuscularly or, well-diluted, intravenously every 15 to 60 minutes until there is a satisfactory response[13] Some believe that it produces only a temporary pressor effect; results in both patients and experimental animals indicate this[35] The drug therefore differs from norepinephrine which produces a direct increase in contractile force, in addition to the pressor effect

PAREDRINE (HYDROXYAMPHETAMINE) This drug is used in doses of 10 mg intramuscularly, or of 5 to 10 mg intravenously

MEPHENTERMINE (WYAMINE) This drug is given in doses of 35 mg. intramuscularly, or of 5 to 20 mg. intravenously, administration may be repeated every 1 to 10 hours Of 18 patients in shock treated with this drug, 7 recovered.[43] In dogs, mephentermine increased the coronary flow, producing a rapid rise in blood pressure without change in heart rate, rhythm, irritability, or output[35]

METHOXAMINE (VASOXYL) Administration of this drug may be started with an intramuscular injection of 15 mg, followed by slow intravenous infusion of a solution containing 35 mg in 250 cc of 5 per cent glucose in water[1]

ISOPROPYLARTERENOL (ISUPREL) This drug has been used in 26 patients, shock was controlled in 7, while in 16 no pressor effect was noted.[41]

USE OF BLOOD AND PLASMA

In extreme shock, with the blood pressure very low or unobtainable, rapid transfusion of blood or plasma (2 to 8 cc per minute) may be started at once.[65] If the blood pressure can be raised to moderate levels, the use of vasopressor drugs may then give the patient a fighting chance for life. Except that it occasionally causes pulmonary edema, blood or plasma transfusion seems to be free from danger; there have been no reports of cardiac rupture due to this procedure.[20, 31] Possibly, transfusions may also have an increasingly important role in the treatment of shock associated with severe peripheral collapse (pooling of blood in the large venous beds, collapsed veins, and poor cardiac filling)[40a]

In shock with low venous pressure (collapsed veins) associated with dehydration (profuse perspiration, vomiting), intravenous infusion of 5 per cent dextrose in saline *solution has been suggested, especially com*bined with vasopressor drug therapy[13]

INTRA-ARTERIAL INFUSIONS Attention has recently been turned to infusions directly into an artery[9, 75] The advantages of this procedure have been described as:[9] (*1*) relatively small amounts of blood are necessary to restore the blood pressure, and (*2*) blood reaches important organs directly The coronary arteries are perfused directly, and important collaterals are opened, there is a rapid return of kidney function; cerebral ischemia is relieved, and the respiratory center is stimulated It is safe to start intra-arterial infusion, even in the presence of pulmonary edema

The beneficial effects of retrograde infusion remain to be proved.[13] In one series, 2 of the 9 patients thus treated survived[71] In another series of 25 patients, shock was controlled in 12, while in 6 no pressor effect could be detected

Ouabain intravenously has been used successfully in 3 of 4 cases of cardiogenic shock in which other measures had failed, 25 to 50 per cent of the usual dose (0 05 to 0 2 mg, instead of 0 5 mg) and avoidance of digitalis are advised[40] The ouabain was used

after the vasoconstrictor agents had been tried, in the belief that if these failed, the glycosides would enhance and support the pressor effect of the drugs

TREATMENT OF RHYTHM AND RATE DISORDERS

Some of the disorders of rhythm and rate in acute infarction may be safely disregarded or require little attention, while others urgently call for the most intensive treatment. Arrhythmias and tachycardias are at times insupportable burdens for the damaged heart. Rapid rates shorten diastole, reduce cardiac rest periods, and increase the work of a heart with an impaired circulation

SINUS TACHYCARDIA AND SINUS BRADYCARDIA

While, in themselves, neither requires treatment, an accurate diagnosis is important Sustained sinus tachycardia is usually associated with extensive infarction, and the treatment should be directed to the underlying cause Reassurance, oxygen therapy, and sedation are always in order

GALLOP RHYTHM

This disorder, as such, cannot be treated Clinically, it should be regarded as manifestation of heart failure

HEART BLOCK AND STOKES-ADAMS SYNDROME

Complete, persistent heart block indicates extensive infarction, and the mortality rate is high Accurate diagnosis is the first step in the treatment Syncopal attacks and convulsions are usually, but not invariably, signs of complete heart block They may be signs of cerebral ischemia due to any sort of rapid rate, usually ectopic Since these cannot be treated like complete auriculoventricular dissociation, every effort should be made to note, preferably by electrocardiography, the nature of the rhythm at the time of the attack. Paroxysmal ventricular standstill is another mechanism which may cause Stokes-Adams attacks.[19]

During a syncopal attack, 5 minims of epinephrine should be given subcutaneously, repeated if necessary at 30 to 60 minute intervals for 1 or 2 doses Isuprel (isopropyl norepinephrine) 0.14 to 0 2 mg subcutaneously, may be substituted,[56] up to 1 mg. may be given, if necessary. Intravenous administration has been proposed for critical situations:[17] 200 μg. in 500 to 1000 ml. of physiologic saline solution or in 5 per cent glucose in distilled water solution, usually started at a rate of 30 to 60 minims per minute, using the ventricular rate as the indication for the rate of titration.[43a] An infusion of 1 mg in 200 ml of 5 per cent glucose has also been used, at a rate of 20 drops per minute.[17] Molar or half molar sodium lactate, intravenously, may restore normal rhythm after all ordinary measures have failed.[7] The rate of injection varies, depending on the urgency of the case, from 50 drops a minute to 250 cc. in 4 minutes The degree of response usually varies directly with the speed of injection. The mechanism of action is still uncertain, but it may be related to the alkalinity of the solution.

In extreme cases, an external cardiac pacemaker, if one is available, may be lifesaving [17 26 84]

Between attacks, ephedrine hydrochloride, 0.20 to 0.30 Gm. (⅜ to ½ grain) every 4 hours, is useful in preventing seizures; this may be combined, if desired, with phenobarbital. Isuprel, 15 mg sublingually, has been proposed as the drug of choice,[56] but in my experience is not as useful as ephedrine or Isuprel parenterally Other drugs suggested for interim treatment are Benzedrex,[21] and paredrine hydrobromide (50 mg. by mouth three times a day, or 20 mg intramuscularly).[29] I have found norepinephrine and barium chloride to be useless.

In patients with Stokes-Adams attacks, rectal stimulation, as by digital examination or enema, should be avoided,[69] it may precipitate severe paroxysms, as in a patient of mine in whom rectal examination or even the use of a rectal thermometer caused convulsions.

First and second degree heart block, in themselves, require no treatment. Atropine shortens the P–R interval, there is no objection to using it, especially since the drug has a beneficial effect on the coronary circulation Anxiety supposedly helps to produce partial heart block,[8] sedation is therefore advisable. If partial heart block alternates with periods

of asystole and the Stokes-Adams syndrome, as it sometimes does, the latter should be treated as outlined above.

EXTRASYSTOLES

Slight cardiac irregularities (extrasystoles, premature contractions, dropped beats) which are harmless in the normal individual are a burden for the acutely damaged heart Furthermore, ectopic beats may be the forerunner of more serious ectopic rhythms. Correct diagnosis is the first step in treatment. Generally speaking, occasional extra beats on the first day of infarction may be disregarded. Since such drugs as digitalis, papaverine, and quinidine may cause extra beats, their administration should be stopped in such cases.

The drug of choice in the treatment of ventricular premature contractions is Pronestyl, 0.25 Gm. by mouth every 4 hours. The dose may be increased to 0 5 Gm if desired Quinidine, 0.2 Gm. (3 grains) every 4 hours, may be substituted if Pronestyl is ineffective.

Although patients with infarction and extra beats seldom complain of thumping or palpitation, as normal persons often do, sedation should be used if they are apprehensive, or perhaps in any case.

PAROXYSMAL HEART ACTION

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA This is rare in infarction; it is usually auricular, rarely nodal Of little moment in normal persons, it is to be feared in acute coronary disease.

Administration of ¼ grain morphine, subcutaneously, is the first step, and often an effective one Vagal stimulation, as by pressing on the carotid sinus or on the eyeball, may be tried at the same time, in acute infarction this should be done gently and cautiously, since there is some question whether this procedure is safe. In any case, morphine sometimes sensitizes the patient to vagal stimulation, so that mild pressure may be effective; the same result is sometimes seen after the use of digitalis

If the patient does not seem to be desperately ill, 3 grains of quinidine sulfate every 4 hours should be used. Pronestyl, 0 5 Gm. every 4 hours, is probably just as effective, and may be tried if quinidine has had no effect.

Digitalis is the drug of choice for the seriously ill patient. This may be given in the form of Lanatoside C, 0.8 mg., followed by 0.4 mg. 1 hour later. Ouabain, 0.5 mg. intravenously, followed by 0.1 mg. every hour up to a total dose of 1 mg. if necessary, is a satisfactory substitute if the physician is familiar with its use.

In refractory cases, especially those associated with shock, 10 mg. methoxamine hydrochloride intravenously, repeated after 30 seconds if necessary, may be tried Neostigmine (Prostigmine) is sometimes successful.

Phenylephrine hydrochloride has been shown to be an effective drug in supraventricular tachycardia.[83] The mechanism of its action is probably twofold (*1*) A cardioinhibitory reflex action mediated through an increase in blood pressure in the aortic and carotid sinuses, and (*2*) a less vigorous stimulatory action directly affecting the myocardium Intravenous administration of 0.5 to 1.5 mg, depending on the blood pressure, has been suggested Administration should be cautious but rapid enough to produce a necessary rise in blood pressure The report states that the drug was effective in 1 patient with mild coronary sclerosis but that it produced short runs of ventricular tachycardia In my opinion, intravenous administration of this drug seems inadvisable for the treatment of paroxysmal tachycardia in a patient with acute infarction unless all other measures have failed and the patient is in danger of dying as a result of the ectopic rhythm.

Use of Atabrine and magnesium sulfate have been proposed, but these drugs are seldom necessary Mecholyl and acetylcholine, effective in normal persons, should be avoided in myocardial infarction Syrup of ipecac or other methods of inducing vomiting, should not be used in acutely ill patients.

AURICULAR FIBRILLATION AND FLUTTER An electrocardiogram should be obtained, if possible, before treatment is begun If the arrhythmia is transient, 3 grains of quinidine every 4 hours should be used, this regimen may be continued indefinitely.

In the patient with an acute myocardial

infarction, the rhythm is more often persistent, rapid, or accompanied by early heart failure. The patient must first be digitalized, and other efforts to restore normal rhythm postponed. In any case, quinidine is more effective at a lower ventricular rate

For the patient who is obviously very ill or whose rate is rapid, a digitalis drug should be adminstered *intravenously* Any one of the following may be used· (*1*) lanatoside C (Cedilanid), 0 8 to 1 2 mg , in an emergency 8 cc (0 8 mg) should be used at once, and 0 2 to 0 4 mg. 2 to 4 hours later; this is the drug I prefer for intravenous use (*2*) Digitoxin, 1 to 1 25 mg , (*3*) strophanthin, 0 25 mg ; (*4*) ouabain, 0 5 mg

If digitalization by mouth is preferred, gitalin or digoxin may be used.

For maintenance, I use 1 or 2 tablets of gitalin or digoxin a day, 1 unit of digitalis leaf may be substituted

When the patient is well digitalized, 3 grains of quinidine every 3 hours for 24 hours or longer should be tried for restoring normal rhythm For patients who have been in congestive failure, it is wise to continue maintenance doses of digitalis throughout the acute course

The treatment, as outlined, often converts auricular flutter to auricular fibrillation Slow auricular fibrillation is so much better than auricular flutter that the clinician can be satisfied when this occurs, even if he has not succeeded in restoring the rhythm to normal by means of quinidine. In about 25 per cent of patients with auricular flutter or fibrillation, the rhythm will revert to normal spontaneously, *even when a 24 hour trial with quinidine* has been unsuccessful

VENTRICULAR TACHYCARDIA This sinister complication of myocardial infarction requires immediate treatment. It may subside spontaneously, especially when it has been induced by digitalis and the drug is withdrawn, but watchful waiting is inadvisable. Although both digitalis and quinidine have been implicated in ventricular tachycardia, their role in causing this arrhythmia is far from certain Nevertheless, if the patient has been taking either drug just before the start of the paroxysm it is wise to stop their use If there is no reason to suspect its responsibility for the ectopic rhythm, quinidine may be used without fear if there is need for the drug. Digitalis must be used more cautiously, but it should not be withheld if it is otherwise indicated [36]

Pronestyl hydrochloride (Procaine amide hydrochloride) is now the drug of choice for ventricular tachycardia, and should be tried first. The drug increases the threshold of excitability and slows down the speed of both auricular and ventricular conduction. Electrocardiographic changes may be noted, transient in most cases, but occasionally persistent, consisting of widening of the QRS complex and of the Q–T interval, and a lowering of the QRS complex and the T waves A study of the pharmacology of the drug noted that neither rhythmicity nor refraction period are altered, nor is contractility affected, in contrast to the effect of quinidine.[79]

The drug is given orally, 1 Gm (4 capsules of 0 25 Gm each) at once, followed by 1 or 2 capsules every 4 hours The patient should be closely watched, and an electrocardiogram taken frequently To prevent recurrence, administration may be continued in doses of 1 capsule every 4 to 6 hours for several days after the cardiac rhythm has been restored to normal

For the patient who appears acutely ill, intramuscular administration is advisable, 1 Gm at once, followed by a similar dose every 1 to 6 hours, as indicated No pain or local reaction occurs. Some believe this method to be the route of choice.[30]

In critical situations, Pronestyl may be administered intravenously, 1 Gm. of the drug *being diluted in 100 cc. of glucose The injection* should be made slowly, not faster than 0 1 Gm. per minute, and the total should not exceed 1 Gm No more than 0 4 Gm is usually required to control paroxysmal ventricular tachycardia, larger doses are needed for persistent tachycardia In one reported series, the tachycardia of all the patients was controlled with 300 to 2500 mg Pronestyl intravenously, and the investigators were convinced of the value of this route [59] Hypotension, at times severe, may occur with this mode of administration, but the drop in pressure is gradual and in the opinion of Pascale and associates concomitant use of norepinephrine permits continued Pronestyl therapy.

Norepinephrine may also be used before Pronestyl administration in patients who are initially in shock. Convulsions occurred in 1 patient in the series, and these investigators now think it advisable to administer 100 mg of sodium phenobarbital before starting Pronestyl therapy.

In addition to hypotension, electrocardiographic changes have been noted when the drug is given by vein; this seldom occurs when it is given by mouth or intramuscularly. Agranulocytosis has been described,[45] chills and fever,[3] rash, ventricular fibrillation,[63] ventricular acceleration,[23] mental changes, convulsions,[39] nausea and vomiting have all been reported. But these toxic manifestations are infrequent, and the drug may be considered as relatively safe when properly used.

The electrocardiographic diagnosis of this variety of paroxysmal heart action is not difficult. However, certain rare disorders of rhythm may simulate it, aberrant interventricular conduction (bundle-branch block) with tachycardia being the most common[75] The diagnosis may not be clear until the heart rate slows and the ectopic rhythm is correctly recognized (paroxysmal auricular tachycardia, auricular fibrillation, auricular flutter, or paroxysmal nodal tachycardia) The differentiation is important, since digitalis may be urgently needed in supraventricular rhythm and is usually withheld in ventricular tachycardia. Pronestyl is a valuable help in the differential diagnosis A report on 5 cases of auricular flutter with bundle-branch block states that the true nature of the rhythm was evident after intravenous administration of 200 to 1,000 mg of Pronestyl[20] The drug should not be used in the presence of complete auriculoventricular block, even if there is complicating ventricular tachycardia Pronestyl depresses both the ectopic focus and the ventricular pacemaking focus in the junctional tissue, a focus of needed ventricular activity[41]

Quinidine should be used if Pronestyl hydrochloride has failed, or is contraindicated for any reason Enselberg[?] believes that quinidine is superior to Pronestyl but most cardiologists do not hold this opinion I find quinidine capricious in action less efficient than Pronestyl, and more hazardous

The exact mode of action of quinidine is still largely unexplained Several it may act on the heart have been suggested (*1*) It prolongs the refractory period of the auricle and decreases the transmission rate of the nerve impulse, both actions resulting from the abolition of vagal tone. (*2*) By direct action on both auricular and ventricular myocardium, it prolongs the refractory period and diminishes the rate of nerve impulse conduction (*3*) It exerts a similar action on the junctional tissue, although to a lesser extent

If quinidine is used, a preliminary test dose of 0 1 to 0 2 Gm (1½ to 3 grains) should be given by mouth, followed by 0 3 Gm (5 grains) every 3 hours, day and night The dose may be increased to 0 6 Gm (10 grains) every 3 or 4 hours. Quinidine should be given by mouth, it is rapidly absorbed and quickly eliminated, so that a cumulative effect need not be feared If oral administration is impossible because the patient is unconscious, it may be administered intramuscularly or intravenously.

Toxic reactions to quinidine are quite common They may be grouped as[51] (*1*) Those due to cinchonism, manifested as nausea, abdominal discomfort, diarrhea, ringing in the ears, and rarely as syncope, convulsions, collapse, and respiratory difficulty, the "allergic" reactions of rashes, purpura, and urticaria (*2*) Cardiac manifestations, consisting of widened QRS complexes, auriculoventricular block, paroxysmal tachycardia, auricular standstill, ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation which is usually transient. The ventricular fibrillation may be the result of the establishment of circus movements in the ventricular myocardium because the rate of conduction is reduced to a greater extent than is the length of the refractory movement, it has been suggested that this is more likely to occur when an acutely infarcted area is especially irritable[4] In ordinary dosage, quinidine has little effect on the coronary circulation[30]

Proceeding under the old adage that desperate ills require desperate remedies, quinidine may be used in ventricular tachycardia in doses known to be toxic It is possible that the use of morphine before quinidine therapy might help to prevent toxic reactions in patients, as it does in experimental animals[41] In some patients, however, quinidine cannot be

1 patient, a woman, in whom as little as 1 grain induced purpura and bleeding within 1 hour, examination of the blood showed total absence of platelets. Similar cases have also been reported.[57]

In the rare cases in which neither Pronestyl nor quinidine can be used, atabrine, 0 3 Gm every 2 hours, may be successful[64] Magnesium sulfate, 20 cc. of a 10 or 20 per cent solution, may be given intravenously, it is without risk but is not very effective. Nupercaine may be tried.[12]

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CHAPTER 16

Anticoagulant Therapy

THE VALUE of anticoagulant therapy in selected cases of acute coronary disease is now widely accepted, although not yet established beyond doubt. Thrombosis and embolism (thromboembolism) account for many of the often fatal complications of acute infarction Numerous reports now attest to the belief that anticoagulant therapy helps prevent these complications and has reduced the mortality rate, but a small group of investigators still feels that this evidence cannot as yet be accepted as valid

As in almost every aspect of coronary disease, the published statistics are of limited value and require the most meticulous study In the early studies, the greatest error was a failure to differentiate between major and minor infarctions, and to separate the patients into those with a good prognosis and those with a high mortality rate However, it is reasonable to expect that a generally acceptable method for selecting cases will soon be at hand.

The most detailed and best controlled report is the 8 year study of the Committee on Anticoagulants of the American Heart Association [70] Others have confirmed these good results, sometimes with qualifications [1, 14, 18-20, 24, 27, 29, 34, 35, 41, 42, 45, 47, 51, 67]. One study reported that the mortality figures were reduced from 25 4 to 14 2 per cent;[55] another, that thromboembolism was found in 25 per cent of untreated patients and in only 5 per cent of those adequately treated,[52] still another, that the incidence of thromboembolism in untreated cases was 31 6 per cent and the mortality rate 23.7 per cent, in contrast to 18 4 and 13 2 per cent, respectively, in those adequately treated.[23]

The American Heart Association's coordinated study of 1031 patients was conducted in 16 hospitals with the cooperation of about 100 investigators A little more than half (589) of the patients were given anticoagulants, while the remainder (442) served as controls Data were collected for 2 years, then evaluated by a central laboratory team consisting of physicians, chemists, and statisticians

Men, of course, greatly outnumbered women, but were afflicted earlier average age of the men, 57 9 years, of the women, 63 9 Of the 16 per cent of patients between the ages of 40 and 49, 87.3 per cent were men, of the 35 9 per cent between 50 and 59 years, 84 6 per cent were men The effects of anticoagulant therapy were striking. 16 per cent of the treated group and 23 4 per cent of the control group died within the period of observation, 23 per cent of the treated group and 42 per cent of the controls had at least one thromboembolic complication before death

The drop in the death rate was confined to the period during which the anticoagulants were effective—from the fourth day of therapy through the fourth day after the last dose During this time, 9 5 per cent of the treated patients died, in contrast to 17 4 per cent of the controls. There were 13 1 thromboembolic complications per 100 treated patients as against 41 8 in the control group

Therapy was beneficial at all ages, but most so in the 50 to 69 year age group, however, anticoagulants did not prevent the upward trend of complications with increasing age. The risk of thrombotic or embolic episodes appears to be somewhat greater in men than in women, but treatment reduces the percentage of complications in both sexes and somewhat more in men than in women. The Committee suggests that this treatment is suitable for patients of either sex and any age,

and concludes that both mild and severe cases will benefit from anticoagulant treatment.

Postmortem examination of patients who died during the study indicated that nearly three fourths of the original infarctions were due to thrombi and therefore "potentially preventable with anticoagulant treatment, provided the need could have been anticipated and therapy instituted in time."

A number of investigators do not accept anticoagulant therapy, as currently practiced, and have raised objections, some of which are unquestionably valid Their objections and reservations have tempered the enthusiasm of other workers and have made for more sensible selection of patients. Rytand[50] has challenged the statistics as a whole, concluding that there is "no valid evidence that prognosis for survival is improved by the use of drugs" Others have emphasized the risks of therapy[6, 8, 11] Still others point out that in a large group of patients with infarction the prognosis is good in any event and that the dangers of anticoagulant therapy may offset the benefits in such instances.[2, 32, 43, 53] Garb[16] summarizes the opposition to the Heart Association Committee report, pointing particularly to the failure to observe "double-blind" precautions and strict alternation of patients

Russek and Zohman[47] reserve this treatment only for the patients they classify as "poor risk," i e, those with (1) previous infarct, (2) intractable pain; (3) extreme or persistent shock; (4) significant heart enlargement; (5) gallop rhythm, (6) congestive heart failure, (7) auricular fibrillation or flutter, ventricular tachycardia, or auriculoventricular block; and (8) diabetic acidosis, obesity, previous pulmonary embolism, varicosities, and past or present venous thromboses. To this list may be added high fever[5,] and azotemia (nitrogen retention)[14]

All these investigators would exclude "good risk" patients from anticoagulant treatment. Russek and Zohman[49] point out that the mortality rate in their good risk patients is 2 45 per cent and that the incidence of thromboembolism is small, they believe that the morbidity and mortality from hemorrhage in dicumarol-treated patients are higher than this figure, and that most of the deaths in the good risk group occur in the first 2 days, i e, before anticoagulant therapy is effective. According to their estimate, only 30 per cent of all patients with myocardial infarction require anticoagulant therapy.

Medical opinion is of course far from unanimous Most clinicians steer a middle course. I prefer to give anticoagulants to all patients for the first 3 days, discontinuing treatment if the prognosis seems good. This seems a more reasonable approach than deciding when the patient is first seen whether he is a "good or bad risk"[21] Every clinician with considerable experience has seen patients with minimal symptoms die, and a "minor episode" with minimal signs become a major infarction within a week. Emboli are found even in good risk patients[96] If the safety of anticoagulant therapy continues to increase as it has done recently, the benefits of treatment will much outweigh the hazards to a worth while extent

ACTION OF HEPARIN AND DICUMAROL

Both heparin and Dicumarol are used principally for their action in preventing the clotting of blood However, other actions are described which may, to a very minor degree, enhance their usefulness in acute infarction

Dicumarol is the proprietary name of 3,3'-methylenebis (4-hydroxycoumarin) The molecular formula $C_{19}H_{12}O_6$ has the structural configuration shown in Figure 98 Our knowledge of this important drug is the result of the work of Karl Paul Link[35] of the Wisconsin Agricultural Experiment Station, who isolated the causative agent of the hemorrhagic disease of cattle, sweet clover disease

Dicumarol prolongs the prothrombin clotting time of the blood plasma In large doses, it increases the coagulation time somewhat,[25] but its therapeutic action is largely based on the hypoprothrombinemia mediated through a toxic effect on liver function It is a trickier drug to use than heparin, and the procedure of administration should be followed attentively Neither Dicumarol nor Tromexan affects the sedimentation rate,[23, 51] nor does Dicumarol, in the dosage currently used, eliminate "erythrocyte aggregation"[4]

It is possible, too, that the beneficial effect of Dicumarol may at least in part be unre-

lated to its anticoagulant action. Dicumarol has also been described as an effective dilator of coronary arteries.[17] It has been claimed that Dicumarol relieves pain in various body areas, produces vascular dilatation, increases the coronary flow, increases the force of heart contraction in the dog, has a possible anti-

action and easy control, and is therefore employed until Dicumarol, a much slower acting drug, becomes effective. Some, however, feel that this precaution is unnecessary and that patients treated with Dicumarol, despite the lag, do just as well as those treated with heparin.[58]

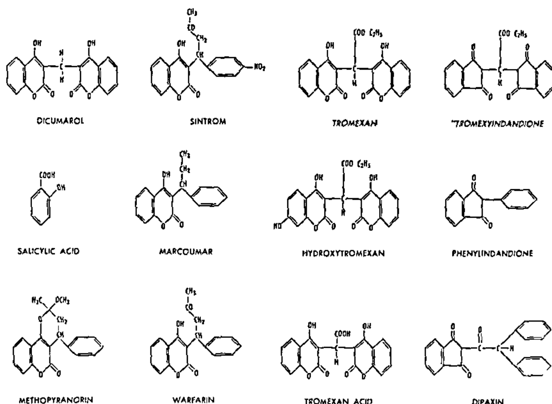


FIG 98 Structure of some of the anticoagulant compounds (Courtesy of Dr Murray Weiner)

pyretic property, speeds the recanalization of thrombi in rabbits, and interferes with the labilization of platelets [16]

Heparin has some action in "clearing" the blood in alimentary lipemia and has been used, with varying claims of success, in the treatment of chronic coronary disease.

Heparin is a dextrorotatory mucopolysaccharide somewhat resembling the connective tissue substance chondroitin sulfuric acid It is considered to be an antithromboplastin, an antiprothrombin, and antithrombin It can be given by vein or muscle but is inactive when taken by mouth. Heparin prolongs the clotting time.

The use of heparin in acute infarction is now confined by most clinicians to the first day or two of illness. It has the merit of rapid

SELECTION OF CASES

The first step in the proper selection of patients for anticoagulant therapy is to eliminate those for whom this type of treatment is contraindicated, regardless of the cardiac criteria, *i e.*, patients with any of the following conditions: (*1*) prothrombin deficiency due to severe hepatic disease or vitamin K deficiency, (*2*) vitamin C deficiency; (*3*) renal insufficiency, (*4*) blood dyscrasias with impairment of hemostasis; (*5*) interruption of continuity of the vascular system, for example, after operations involving (*a*) the brain or cord, (*b*) raw surfaces, (*c*) tube drainage, (*d*) jaundice; (*6*) late pregnancy, (*7*) subacute bacterial endocarditis.[62]

My own practice is to use anticoagulants for all patients with major myocardial infarction unless conditions other than heart disease contraindicate their use. However, I would forego this treatment in all cases of minor infarction unless they fell into the "poor risk" group otherwise I would therefore give anticoagulants to patients with minor infarction who have or have had heart enlargement, conduction or rhythm disorders, diabetic acidosis, varicosities, other evidences of venous thrombosis, or embolism. Thus, while following the lead of the minority group in excluding some patients with acute coronary disease, I have been broadening their base considerably. The hazards of anticoagulant therapy in experienced hands are now so few that a patient should not be deprived of this method of preventing serious complications The occasional patient who seems to be doing well but in whom an extension of the infarction or some other thromboembolic complication develops during the first 2 weeks of his illness is commonly seen. Löffler and Schnebli[33] point out the frequency with which "good risk" patients become poor risks after a few days, they do not restrict therapy to the "poor risk" group

Pregnancy need not be considered an absolute contraindication to anticoagulant therapy. One pregnant woman with myocardial infarction was treated for 2 months with no untoward incident.[88]

A third method of dividing patients with myocardial infarction into categories, that of the presence or absence of hypercoagulability of the blood, may help the clinician to select patients for anticoagulant therapy The blood of many patients with early myocardial infarction is hypercoagulable, and these patients should be treated promptly. Lenegre and Beaumont[29] found an increased clotting tendency in 24 of 26 persons with "impending infarct," and obtained excellent therapeutic results with anticoagulants It seems to me that the evidence rather points to hypercoagulability as a response to an established thrombus and that these cases of "impending infarct" already had small infarcts, nevertheless, a major infarction may have been avoided This is a further argument in favor of using Dicumarol even in "minor occlusions" Peel selects his patients for anticoagulant therapy according to their heparin retarded coagulation time [124]

TECHNIC OF TREATMENT

Anticoagulant treatment should not be started until the patient has been thoroughly examined and possible contraindications ruled out. A reliable laboratory must be available and tests must be done as often as the physician advises, usually daily including Sunday. Dicumarol should *never* be given until a control prothrombin time is obtained

The Link-Shapiro modification[70] of the Quick method for determining the prothrombin time is entirely satisfactory, and is the method used by most of the hospitals cooperating in the Heart Association survey [70] The whole plasma method is the only one needed in ordinary clinical practice, but some centers use the 2.5 per cent dilution test. The normal value for whole plasma is 13 to 17 seconds, for diluted plasma, 35 to 52 seconds All prothrombin times referred to in this text were obtained by the Link-Shapiro whole plasma technic.

Once the decision is made to use anticoagulants, several steps are essential

1. Determine the patient's prothrombin time, and preferably the coagulation time

2. Start heparin at once, 75 mg intravenously every 6 hours until a satisfactory Dicumarol response is obtained This step may be omitted, but if heparin therapy is to be employed at all, no time should be lost since the risks of treatment are small I do not continue heparin beyond 48 hours, nor can I recommend intramuscular administration, which is often painful and of irregular action

3 If the prothrombin time is normal, give an initial dose of 300 mg Dicumarol at once The dose on the second day is usually 200 mg. If the initial prothrombin time is over 20 seconds, anticoagulant therapy should not be started.

4 Determine the daily dosage thereafter on the basis of the prothrombin time Blood may be drawn at any time of day, but preferably at the same time each day; fasting specimens are not needed. With the use of the newer, highly standardized thromboplastin, reliable prothrombin times can be expected from any

competent laboratory; the competence of the technician, however, should be ascertained. The aim is to reach a whole plasma prothrombin time roughly two to two and a half times that of the control time The following schedule is a satisfactory rule of thumb:

Time	*Dose*
25 sec or less	100–200 mg
25–30 sec	50–100 mg
30–35 sec	50 mg
35 sec or more	Withold the drug

5. Treatment should extend throughout the period of hospital confinement but in no case for less than 4 weeks after the beginning of the attack Should further thrombosis or embolism occur, treatment should not be discontinued until 4 weeks after the last such incident If long-term anticoagulant therapy is to be instituted, it may follow this 4 week period without break

COMMENTS It is better to report prothrombin time in seconds rather than percentages

The risk of serious hemorrhage is now extremely small, provided all precautions are observed and the laboratory facilities are good In the past 2 years no serious bleeding has occurred in any of my patients However, the possibility of hemorrhage is always present, and the physician should be prepared with countermeasures Occasionally, the prothrombin time rises in a patient who degrades Dicumarol slowly, and sometimes it rises for no evident reason If the time is 60 seconds or less, there is no cause for alarm unless there are signs of bleeding If the time is over 60 seconds, anti-Dicumarol treatment should be instituted.

ALTERNATE METHODS OF ANTICOAGULANT THERAPY

The intermittent maintenance dose method introduced by Shapiro may be used by those who have had experience with it and when it is impossible to obtain daily prothrombin time estimations [55] It is particularly suitable for long-term therapy The usual initial dose of 300 mg of Dicumarol is given on the first day and the prothrombin time is measured every second to fourth day. In my opinion, it is wiser to obtain readings daily for the first week or two. Half the initial dose is given when the prothrombin time is decreasing, *i.e.*, after the peak response to the preceding dose has passed The response to similar doses, administered after successive peaks are passed, is noted With this schedule, Dicumarol is usually given every 5 to 7 days The reaction to Dicumarol varies; some patients are sensitive, some very resistant. Once the patient's pattern of response is established, the intermittent dose method is useful since cumulation is avoided and fewer laboratory tests are needed

TREATMENT OF OVERDOSAGE

Vitamin K_1 is effective in reversing the effect of Dicumarol, Tromexan, and drugs of the phenylindanedione series. Bleeding is checked within 3 to 6 hours and the prothrombin time returns to normal within 4 to 12 hours The oil-soluble vitamin K_1* is much preferable to the synthetic water-soluble naphthoquinones which have a lower vitamin K activity and are not as reliable in correcting *anticoagulant-induced hypoprothrombinemia* In a bleeding emergency, 50 to 150 mg are given slowly by vein, 50 mg are used to reduce a dangerously elevated prothrombin time

Vitamin K_1 by mouth has recently been found effective [9, 15] Doses as low as 1 to 20 mg are apparently as satisfactory as the larger intravenous doses generally recommended, and in about the same length of time It would be a significant advance if the experience of these groups were to be confirmed, since no refractoriness to anticoagulants has been noted after the smaller amounts, after larger doses given by vein, it may take several days of anticoagulant therapy to bring the prothrombin time to a satisfactory level. I have used this method with good result in patients whose prothrombin time I considered undesirably high; I have not had the occasion so far to use it for actively bleeding patients

COMPLICATIONS AND RISKS

The most serious complication is hemorrhage Though this may be very slight, per-

* Mephyton-Merck.

haps no more than a few red blood cells in the urine, it should never be disregarded, the anticoagulants should be stopped, at least temporarily. The risk of hemorrhage is minimal, provided the necessary precautions are observed. Nevertheless, because laboratories and the reagents they use are still fallible, and there are great individual variations in the metabolism of Dicumarol, bleeding occurs occasionally. It is said that the danger of overdosage is greater during periods of excessively hot weather because of dilatation of peripheral vessels and rise in the blood level of the drug when insufficient fluids are taken.[57]

Hemorrhagic complications, most often in the brain, gastrointestinal tract, and pericardium, were listed as causing 122 deaths.[49] Bleeding into the pericardial sac, with or without cardiac rupture, seems to be more frequent since the advent of anticoagulant therapy; it has received particular attention ever since its first description in 1949.[23] A number of cases have been reported, including several in which the patient recovered when cardiac tamponade was relieved by pericardiotomy.[23, 45, 60] Waldron and associates,[64] in a detailed review, report that between 1946 and 1951 at the Massachusetts General Hospital 12 cases (4 98 per cent) of cardiac rupture with hemopericardium were found among 241 cases of infarction not treated with anticoagulants which came to autopsy This was in startling contrast to a group of cases treated with anticoagulants; in 71 of these, 10 ruptures were found at autopsy, an almost threefold increase In the same series, 25 had blood in the pericardial sac without rupture, 11 (4 6 per cent) in the untreated series, 14 (19 7 per cent) in the treated series. These investigators felt that the presence of blood in the pericardial sac was an incidental finding in most of the cases, they held anticoagulants responsible for only 1 of the 14 deaths

The experience of the Committee on Anticoagulants of the American Heart Association is similar, though based on a smaller number of autopsies[59] Of 48 untreated cases, examined postmortem, 2 (4 2 per cent) had hemopericardium without rupture and 4 (8 3 per cent) with rupture, 3 of the latter were septal ruptures without blood in the pericardial cavity. Of 41 treated cases, 5 (12 2 per cent) had hemopericardium without rupture and 8 (19 5 per cent) with rupture. By combining the data of the two series, the number of cases without anticoagulants totaled 289, of which 13 (4 5 per cent) had hemopericardium without rupture and 16 (5.5 per cent) with rupture, the treated group totaled 112 cases, of which 19 (16 9 per cent) had hemopericardium without rupture and 18 (16 1 per cent) with rupture

In the Massachusetts series, the incidence of this complication appeared to correlate with the degree of anticoagulant effect In those who had had less than therapeutic levels, pericardial blood was found in 7 of 28 (25 per cent), at therapeutic levels, in 11 of 32 (34 4 per cent), with excessive anticoagulant, in 6 of 11 (54 5 per cent). A noteworthy feature of this series was the fact that in both treated and untreated groups the incidence of mural thrombosis seemed to be the same (60 per cent)

One can scarcely escape the conclusion that while anticoagulant therapy may reduce the total mortality and morbidity rates in infarction, more of the patients who do die will be found to have hemopericardium The Heart Association's Committee concludes as follows

> It seems safest, therefore, to base their clinical practice on the expectation that anticoagulants may increase somewhat the frequency and severity of hemorrhage, the risk of myocardial rupture and hemopericardium, with cardiac tamponade Alertness on the part of the clinician and good management of anticoagulant therapy can minimize these risks Therefore the physician using anticoagulants should not only supervise such therapy with care but also should be equipped for the clinical recognition and treatment of cardiac tamponade and other hemorrhages both in and outside the heart

Hemopericardium should be suspected if the patient's general condition deteriorates, especially if there are narrowed pulse pressures, distended veins, friction rub, and anemia[23]

SUBSTITUTES FOR DICUMAROL

The care with which Dicumarol must be administered has led to a search for improved substitutes, one of which may eventually replace Dicumarol as the most popular anti-

coagulant The formulas for some of these are given in Figure 106.

Coumadin sodium is a sodium derivative of Warfarin [3 (a-acetonylbenzyl)-4-hydroxycoumarin] It is marketed in tablets of 25 mg each or in ampules of 75 mg Warfarin itself is a Dicumarol analogue prepared by Link,[31] it was first introduced as an agent for rodent control, and later was adapted for use as an anticoagulant by Shapiro[64]

According to Link, the sodium derivative has the following characteristics (*1*) its solubility in water is 75,000 greater than that of Dicumarol, (*2*) it can be given intravenously, (*3*) relatively small doses are clinically effective and their effect appears earlier than with Dicumarol, (*4*) risk of hemorrhage with overdosage is slighter than with Dicumarol, (*5*) it yields a smooth extended curve of hypoprothrombinemia (expressed as prolongation of prothrombin time), (*6*) vitamin K_1 readily counteracts toxic effects

There seems to be very little difference whether the initial dose is given by vein or by mouth[43] The usual dose of 75 mg is effective in 21 hours when given intravenously and in 24 hours when given orally Investigators at the University of Wisconsin, who have expressed enthusiasm for Coumadin sodium, give 1 mg per kilogram of body weight, but not exceeding 75 mg as the initial dose, the maintenance dose, depending on the prothrombin time, is 12 5 or 25 mg every day to every third day, none being administered if the prothrombin time is over 25 seconds[9] In another series of 100 patients, the results were so good that the drug was considered the anticoagulant of choice[43] No toxic reactions have been noted in the blood, urine, or liver, although microscopic hematuria occurs occasionally Hypersensitivity was shown by 3 patients, one of whom had metastatic cancer of the liver[9]

Tromexan [ethyl bis(4-hydroxycoumarinyl) acetate] is a coumarin derivative. It is also known as Palentan Appendix A of the Heart Association Committee's report[70] reviews a comparative study of Dicumarol and Tromexan, and lists the pertinent literature

Tromexan is claimed to be one sixth as potent as Dicumarol and only one twentieth as toxic. Its action is more rapid, a therapeutic level being achieved within 20 to 30 hours When the drug is discontinued, the prothrombin level rises promptly, usually reaching normal levels between 24 and 48 hours. Its speedy onset of action and the reversibility of its effect make Tromexan worth consideration

The initial dose is 1500 mg, but 1800 mg may be given if the patient's weight is more than 180 pounds and his condition is good The average daily requirements run from 300 to 900 mg., in divided doses. Daily prothrombin tests should be done.

Judging from the Committee's report and from my own experience, there seems to be no great advantage in using Tromexan rather than Dicumarol. Rapidity of response can be achieved, if it is considered important, by using heparin. The ease with which the effect of Dicumarol can be reversed with vitamin K_1 makes the slower decrease of its effect when withdrawn no great liability However, many careful clinicians are using Tromexan with satisfaction.

2-Phenyl-1,3-indanedione (Danilone, Hedulin, Dindevan) is a synthetic anticoagulant first described for clinical use by Soulier and Gueguen[67] The drug is a water-insoluble yellow powder which interferes with prothrombin production[7, 44, 44a, 62, 63, 66, 66a]

The first day's dose is 300 to 500 mg, doses of 100 to 200 mg are given on subsequent days.[5] The prothrombin time rises to two or three times normal within 48 hours and returns to normal within 2 days after treatment is discontinued Earlier reports indicated that the drug produced no deleterious effects on liver function, sedimentation rate, and platelet and differential blood counts,[5] more recently, however, depression of the leukocyte count has been reported[36] An annoying but probably inconsequential reddish metabolite may appear in the urine Its action seems intermediate between that of heparin and Dicumarol, but closer to the latter. So far, this drug does not seem to be strikingly better than more familiar anticoagulants, although some observers consider it the drug of choice.

2-Diphenylacetyl-1-3-indanedione (Dipaxin) is described as a potent hypoprothrombinemic drug with few toxic effects, eminently suitable for long-term therapy.[12]

Nitrophenyl acetyl-ethyl-4-oxycumarin (*Acenocoumarin; G-23350, Sintrom*) is currently under intensive investigation as a Dicumarol substitute. It is said to be an anticoagulant of low toxicity in animals, with

a speed of action intermediate between Dicumarol and Tromexan. The dose required to induce a therapeutic level varies from 20 to 28 mg; the daily maintenance dose averages 2 to 6 mg. The prothrombin time curves induced are reported to be surprisingly free of fluctuations My limited experience so far confirms the first favorable preliminary reports. Sintrom is effective in small doses and strikes a balance between slow- and fast-acting anticoagulants[81a]

LONG-TERM ANTICOAGULANT THERAPY

Early reports on this method of handling chronic coronary disease have been optimistic enough to warrant further trial.[33, 46, 55, 69] So far, this regimen has been used largely as an extension of short-term therapy for patients with infarction in an effort to prevent recurrence The aim is to prevent those infarctions which result from thromboses within the coronary arteries. Probably over half of the recurrent infarctions are caused in this way; the Heart Association Committee estimates the figure at about three fourths. It is possible, of course, that in a good number of infarctions in which there are no clots in the major arteries, clots may be present in small but critically important collateral vessels It is improbable that anticoagulants prevent atheroma as such, unless Duguid[10] is correct in supposing that clotting precedes atherosclerosis. At the moment, long-term treatment of this kind is largely empiric and can be judged only by the results obtained by responsible investigators

When Dicumarol is used during the acute phase of an infarction, prothrombin times are determined daily for several weeks At the end of that time, a pattern of patient response will have emerged as a rule, and laboratory determinations will be needed only once or twice a week to establish dosage. In some cases, the tests need be done only every 2 to 4 weeks. In some patients, however, no pattern becomes evident, and the degree of hypoprothrombinemia will seem to bear little relation to the amount of drug given The hazards of therapy in such patients will outweigh the benefits, and long term treatment should not be undertaken There is no evidence that the prolonged use of Dicumarol damages the liver or kidneys[70]

Several important series of patients on this regimen have been reported In one, 1100 patients were observed for 6 months to 8 years; 30 per cent discontinued treatment and 16 per cent died during the treatment period[51] Fresh transmural infarctions were seldom found at autopsy in the latter, the cause of death was usually ventricular fibrillation or standstill, decompensation, or acute coronary insufficiency with focal myocardial necrosis Amelioration of anginal pain was common Hemorrhage occurred in 25 per cent, but only rarely was it severe or the cause of death It was concluded that this form of treatment prevented recurrence and prolonged life in many patients, as judged by comparison with a control group of 500 patients

In a South African series of 82 patients most were treated by Dicumarol, a few were given phenylindanedione[52] The prothrombin time, determined at biweekly intervals, was maintained at approximately twice normal levels. The group treated consisted of those with repeated infarctions and those more severely ill than a control group of 88 patients In a period ranging from 1 to 6 years, the mortality rate was 7 3 per cent and there were 7 recurrences in the treated group, as against a mortality rate of 33 per cent and 24 recurrences in the control group

Investigators at the New York Hospital[13] have reported on two groups of patients The first, consisting of 11 patients who had had 2 or more episodes of infarction, were observed for 587 patient-months without anticoagulant treatment, during which time they had 49 episodes of thromboembolism, including 30 myocardial infarctions, after being put on anticoagulants, there were only 3 such episodes in the subsequent 393 patient-months The second group of 12 patients had had only one infarction each and were treated for 554 patient-months, during which time there was only one questionable thromboembolic incident In all, some 300 patients (rheumatic heart disease, thrombophlebitis, infarction) received long-term anticoagulant therapy Dicumarol or Tromexan was given in sufficient dosage to result in a prothrombin time of 25 to 35 seconds Determinations of the prothrombin level were done about once a week Complications were few There were 31

hemorrhagic complications, mostly minor, in 85 patients during 3628 patient-months of treatment.

Other investigators, too, are convinced of the value of long-term anticoagulant therapy. In patients with a single infarction or with angina, the death rate was three times greater during an observation period of 6 months to 5 years in the untreated than in the treated patients In the group with more than one episode of infarction, the death rate in the control group was five times as high as in the treated group, minor hemorrhagic manifestations occurred frequently, and serious ones occasionally

My own experience has thus far been too small to permit final evaluation. Long-term treatment was at first reserved for patients with multiple infarctions in whom the prothrombin time could be easily controlled Encouraged by recent reports, I have begun to use this regimen for "first attack" patients who are cooperative and intelligent, provided they do not require prothrombin time determinations too frequently

SPECIAL PRECAUTIONS IN LONG-TERM THERAPY

The greatest obstacle to the use of anticoagulants is the wide range of sensitivity and of patient response. Careful study of the patient's reactions to the chosen drug usually, though not invariably, leads to a safe treatment schedule In long-term management, other factors must also be considered, such as. (*1*) reduction of the amount of vitamin K in the diet; (*2*) presence of diarrhea or biliary obstruction, both of which affect the absorption of the vitamin, (*3*) administration of antibiotics by mouth, which may inhibit vitamin K–producing organisms in the bowel, and, (*4*) simultaneous administration of other drugs, such as salicylates Any of these call for special vigilance and more frequent determinations of the prothrombin time.

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CHAPTER 17

Management of Angina Pectoris and Chronic Coronary Disease

GENERAL MANAGEMENT

THE GENERAL treatment of angina pectoris and that of postinfarctive or other chronic coronary disease are broadly the same, but the presence of angina presents special, superimposed problems

It is difficult to decide what and how much the patient should be told about his illness. The patient with true angina is usually aware that he is suffering from a heart ailment, and the physician is therefore well advised to acknowledge this and start his advice from that point The spasmodic nature of angina pectoris and the fact that the outlook is relatively good can be emphasized The comparison of anginal pain to the clenching and unclenching of a fist is a useful analogy, since it coincides so well with what the patient feels I have also found it advisable to show the patient a sketch of the coronary circulation; *the intelligent layman can understand this* and is helped by the feeling that there is no *special mystery* about his illness Figure 99 shows a useful diagram available in pads so that a sheet may be handed to the patient.

It is most important that the patient be warned to notify his physician of any sudden increase in pain or change in its nature A shift in the radiation of the pain, or a lack of relief *with the usual rest or medication must* be reported at once The patient must know that if 1 nitroglycerin tablet fails to relieve his pain as usual, a dozen tablets will not do so Attention to this warning may help to identify early "twig" occlusion, and may prevent major infarction

In general, a patient's condition will improve if his personal life is happy, every

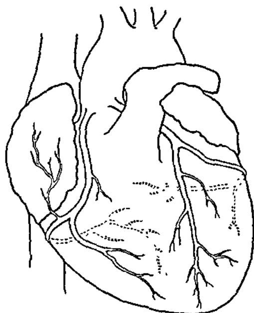


FIG 99 Diagram of the coronary circulation which may be given to the patient (Courtesy of Dr J J Kralik, Marymount Hospital Cleveland, Ohio)

effort should therefore be directed to make the patient and his family understand this Frank discussion has sometimes lead to striking improvement in avoiding minor frictions which had existed for years. The patient's business life can at times be adjusted in the

same way; only rarely is a change in occupation needed This is, in effect, the sort of surface psychotherapy which any understanding physician can use Some patients, however, need more thorough psychiatric treatment, and the physician should guard against assuming the role of the psychiatrist. The trained specialist in this field may help even the patient with advanced organic heart disease, and it is he who should undertake this part of treatment,[15] in cooperation with the physician.

Often, the patient states that some special form of activity or strain induces an attack or makes him more susceptible to seizures, for example, overeating, the use of some special condiment or stimulant, bolting his lunch, Sunday bowling, or lifting packages. When this information is not volunteered, a carefully taken history may disclose the existence of a "trigger mechanism." If the trigger cannot be avoided, nitroglycerin may be used prophylactically

REST AND EXERCISE

Once the patient understands his illness, he may be able to manage his rest and exercise without much help from the doctor. He must *be taught in the early days of his illness that* rest is the most important item in the treatment of his pain He must also learn to resist the temptation, so common in the beginning, to "work off an attack" He must stop what he is doing when a seizure comes on Most patients do not need prolonged periods of bed rest, and prescribing such rest is to risk a serious breakdown in morale An occasional short vacation, in bed or otherwise, may be of the greatest value, however Even patients with mild coronary disease benefit from returing early and getting up as late as possible

Outdoor exercise, except in the cold or wind, is beneficial for the patient with angina, as with any other heart disease Graduated exercise is useful if the patient goes about it sensibly, and exercise tolerance may improve noticeably. A trip to a spa is sometimes desirable. In a new environment, the patient relaxes and the baths and exercises under competent supervision may help physically and in other ways Many patients can play golf if a caddy is employed and the more rugged courses are avoided On the other hand, swimming, especially in unguarded areas, tennis, and handball should not be permitted

DIET AND GASTROINTESTINAL TRACT

The stomach is one of the most important trigger areas for cardiac pain The patient with angina pectoris must avoid overeating and rapid eating, and those who are habitual air swallowers must be warned to eat more slowly Charcoal, peppermint, or some other carminative mixture may be used if meals are followed by distention Mistura nigra, first suggested to me by Dr Harold Hyman, is very effective for flatulence

Ol menth pip	
Pepsin aa	1 0
Sodium phenobarbital	0 6
Carb lign.	6 0
Glycerine	20 0
Aqua q s ad	120 0
"Shake Well" label	

Sig 1 teaspoonful in ⅓ glass of water t i d p c

Dietary measures with regard to the metabolism of lipids are discussed in Chapters 4 and 20

Constipation should be controlled in the simplest possible manner, preferably by diet Milk of magnesia, a half ounce at night, or an emulsion of mineral oil with agar agar or milk of magnesia, is helpful.

TRAVEL

FLYING The patient with coronary disease may travel by air, provided the plane is pressurized and has emergency oxygen equipment on board[14] In certain circumstances, flying may be the least fatiguing method of travel Certain exceptions must be made (*1*) Generally, travel by plane during the acute phase of infarction is inadvisable, although I have known several who did travel without untoward incident (*2*) No one with a history of coronary disease should be permitted to pilot a plane (*3*) Patients who have never flown and are apprehensive about the prospect, and those who have experienced precordial pain during flight should be advised against air travel

DRIVING Patients suffering from chronic coronary disease or angina pectoris should not expose themselves to the exasperations of

driving in heavy city traffic, or to the strain of driving at high rates of speed. If possible, they should have the benefit of power steering. The emotional reactions to driving vary with the individual; one who is readily annoyed or fatigued should take only easy drives on unfrequented roads. It must be impressed on every patient with a cardiac disorder that he must pull off the road and stop driving as soon as he feels even the slightest cardiac pain. Joining an automobile club or making other arrangements for emergency service is a wise precaution, the patient must not undertake anything involving excessive strain, such as tire changing or extensive repairs, especially in cold weather. If all these safeguards can be observed, the patient need not be discouraged from driving a car for himself. But driving a truck, bus, or other vehicle for hire is another story. I do not permit my patients to continue this type of driving, for the lives of others, often many, are involved. Human frailty being what it is, a man whose job is at stake is often reluctant to abandon a trip when he doesn't feel completely well. In my experience, most industries cooperate in assigning such patients to other jobs.

SEXUAL RELATIONS

If no pain, dyspnea, or excessive fatigue is experienced after or during sexual intercourse, the patient need not be burdened by many instructions or restrictions. Almost all patients may be given the general advice that sexual relations be conducted "in a leisurely fashion," and not more often than twice a week. Coital angina may be alleviated or abolished by the precoital use of nitroglycerin. Sedation may be used for patients with satyriasis or excessive sexual libido. When sedation is unsuccessful, estrogen therapy invariably diminishes sexual drive, whether the libido is heterosexually or homosexually directed. I have used Premarin with great benefit in 3 homosexual patients with infarction who were annoying male nurses with their attentions.

DRUG THERAPY

NITRITES

The rapidly acting nitrites are the most important drugs in the treatment of angina pectoris. Only amyl nitrite and nitroglycerin need be considered. The effect of amyl nitrite is rapid, but the drug is more expensive, more troublesome to use, and is a liquid with a pungent odor. Its odor and its method of administration (crushing an ampul in a handkerchief) may make the patient unpleasantly conspicuous.

Nitroglycerin, a more useful drug, is administered in the form of tablets placed under the tongue. The initial dose should be 1/200 grain, and usually suffices for most patients throughout their illness, 1/150 or 1/100 grain may be needed, but the smallest useful dose should be sought. Dizziness, headache, faintness, palpitations, and rarely syncope are some of the side effects which may result, especially at first; the patient should therefore be advised to sit or lie down while taking nitroglycerin the first few times. Often, the unmelted portion of the tablet can be discarded as soon as relief is obtained. Nitroglycerin is not a habit-forming drug, the patient should be reassured on this point, so that he need not fear the possibility of drug addiction.

Nitroglycerin is highly useful in preventing attacks of pain. The regular use of nitroglycerin two or three times a day will keep some patients free from attacks. Others can avoid angina by taking a tablet of nitroglycerin before performing some accustomed effort known to produce pain. While this is of course desirable, there is no justification for using this drug to make strenuous activities possible.

The nitrites may have to be used for diagnostic purposes, in such cases, only small doses should be given, and the drug discontinued promptly if relief is not obtained. Overdosage with the nitrites may be harmful.[80, 103] They may cause headache, gastric irritation, methemoglobinemia, and depression of renal function,[110] they also have a tendency to cause an increase in intraocular and intracranial pressure. Nitroglycerin decreases heart volume and stroke volume through venous pooling and reduced blood return to the heart.[16] In about 10 per cent of patients, this action sufficiently reduces coronary blood flow, despite continuing coronary vasodilation, to give a positive result in the Master two-step test.[94]

Prolongation of the action of nitroglycerin has been attempted. Nitroglycerin in oil has

been put into gelatin capsules (Glonoral); several of my patients have reported some improvement, but my experience with this preparation is small. Nitroglycerin has recently been put up in a 2 per cent ointment, the first report on its use indicates that some patients have been helped, but the authors warn that sudden withdrawal of the ointment may produce acute coronary insufficiency.[23]

A most promising approach is the newer one of compressing tiny, specially coated granules containing nitroglycerin into a tablet designed for uniform release of the medication over an 8 to 10 hour period. These tablets are marketed as Glytrime* or Nitroglyn, each containing 1/25 grain. Of over 100 cases so far treated, over 60 per cent have reported a reduction in the number of sublingual tablets needed through the day. As yet I have used these tablets only for patients who need nitroglycerin regularly. Treatment may be started with 1 tablet morning and night, and increased to three times a day if necessary. Some patients may require a higher dosage, and for these the 1/10 grain tablet of Nitroglyn may be used. Headache or vertigo are noted occasionally, especially with the larger dosage, but on the whole this type of "slow-release" nitroglycerin seems to provide a distinct advance in the treatment of some patients.

Several slower acting nitrites have been tried: inorganic compounds, such as sodium nitrite and bismuth subnitrate, and organic compounds such as mannitol hexanitrate. Most of these are of little use in treating angina pectoris, although all liberate the nitrite ion in the body. Sodium nitrite may even have an adverse effect on cardiac pain.[86] Triethanolamine trinitrite biphosphate (Metamine) has been reported as a promising drug.[40a]

The most effective drug in this group is pentaerythritol tetranitrate, which I have found to be useful for reducing the intake of nitroglycerin, especially in angina decubitus and postprandial angina.[77] Others have confirmed these findings. In one series, this drug was found to be the most effective of several tested.[92] The drug is absorbed sublingually and as a dust by the pulmonary epithelium, and apparently dilates the coronary arteries in both man and experimental animals; it seems far more effective than triethanolamine trinitrate in warding off anginal attacks.[113] The lowest death rate and the lowest incidence of thromboembolic complications in infarction were found by Kissane and associates[61] in patients receiving pentaerythritol tetranitrate. Some workers have been unable to confirm these reported beneficial effects,[67, 106] but my colleagues and I find it to be the most useful of the slower acting organic nitrites. Still others found significant improvement in only 25 per cent of patients and equivocally favorable reactions in 55 per cent, but concluded that the drug was worth trying and might, in 25 per cent of patients with angina, mean the difference between relative freedom from symptoms and a prolonged illness with much suffering.[89] Pentaerythritol tetranitrate is given in 10 mg. doses before meals and, when necessary, at bed time. In severer cases, the dose may be increased to 10 mg., or phenobarbital, 0.015, may be added. We have recently had gratifying results from the addition of nitroglycerine, gr. 1/200th, and rauwolfia serpentina, 0.1 mg., to 10.0 mg. of pentaerythritol tetranitrate, given in a single tablet (Pentte-Carnrick) before meals and at bed time. This combination takes advantage of the prophylactic effect of nitroglycerine and the sedative action (and possibly specific action on the angina)[60a] of rauwolfia. The tablet has the further advantage of dissolving quickly under the tongue and can be used if the patient has one or two anginal seizures during the day. In our experience so far, the number of anginal attacks has been sharply reduced in about 70 per cent of patients dependent on nitroglycerine.

* Nitromed (R) is identical to Glytrime in composition.

The nitrites were introduced into the treatment of angina pectoris by Lauder Brunton in 1867. Nitroglycerin was used first in 1879 and sodium nitrite in 1883. The nitrites relax smooth muscle, the effect is most marked in the finer blood vessels, especially the coronaries, where the dilatation seems to last longer than in other vessels. The action of the nitrites is independent of the nerve supply of the muscle. All the vessels of the body take part in the vasodilatation and the effect is most marked on the postarterial capillaries.

The nitrites increase the coronary blood flow in dogs by from 30 to 100 per cent.[32] The effect is striking and may be easily seen on the surface of the heart.[32] Weiss and Ellis[119] believed that nitroglycerin produced no increase in cardiac output, indicating that there was no direct effect on

the myocardium Wégria and associates,[109] who found an increase in the cardiac output per minute, in the systolic output, and in heart rate when there is no change in the blood pressure, concluded that while cardiac work is increased, anginal pain is relieved because the increase in coronary flow is relatively greater than the increase in cardiac work. Raab and Lepeschkin[83] believe that the therapeutic effect of nitroglycerin is not mediated via coronary dilatation but rather by interference with the metabolic anoxia-producing effects of sympathomimetic amines on cardiac muscle. On the other hand, Eckstein and co-workers[27a] hold that the effect of nitroglycerin is not antiadrenergic.

Eckenhoff and Hafkenschiel[27] have shown that the intracoronary injection of nitroglycerin in anesthetized dogs increases coronary flow except if the dose is so large that when it reaches the systemic circulation it produces marked hypotension, with resultant decrease in coronary flow This of course has important clinical implications

SEDATIVES AND ALCOHOL The most useful drugs in the treatment of angina after, or perhaps including, the nitrites, are probably the sedatives Any mild sedative, such as phenobarbital or chloral hydrate, will help relieve the tension and anxiety which almost always accompany this illness, especially in the earlier stages Morphine, Demerol, and other habit-forming drugs should be avoided; the dangers of addiction are very great indeed.

Heberden recognized the beneficial effect of ethyl alcohol and he mentioned it in his first report Although it has been claimed that small doses of alcohol dilate the coronary arteries,[25, 111] this has been challenged [90] There can be little doubt that alcoholic beverages are credited by many patients with contributing to their well-being and diminishing their cardiac pain. It is probable that alcohol is merely a quick-acting sedative, but there is no reason for depriving a patient of its benefits. The danger of addiction seems small, when compared to the pleasure it gives the patient. Any acceptable form of alcohol may be used, such as spirits before meals or wine at any time.

XANTHINES

The xanthines have been popular in the treatment of angina pectoris for many years, and some patients feel that they are of help. Theophylline ethylenediamine (aminophylline) is the preparation most often used in this country; it is given in 0.20 to 0 30 Gm. doses three or four times a day, sometimes combined with small amounts of phenobarbital. Good results have recently been claimed for choline theophyllinate [4, 26] I have not yet used this compound in a large enough number of patients, but I have found the other xanthines mildly effective in only a small percentage of patients, and have gradually stopped using them.

Clinically, most xanthine compounds have been found of little value in the treatment of coronary disease, and are now being generally abandoned The Council on Pharmacy and Chemistry of the American Medical Association[1] has also concluded that the clinical evidence for their favorable action is inconclusive and the potential benefit slight, but that they "could be tried in selected cases whenever myocardial stimulation would not be harmful"

The xanthine group of drugs are methylated derivatives of xanthine dioxopurine, caffeine being the most familiar member. There is no uniformity of opinion regarding their action on the heart and coronary vessels in either experimental animals or man. Most of the evidence has been summed up by Wégria and his colleagues [109]

PAPAVERINE AND OTHER DRUGS

PAPAVERINE The evidence for the effectiveness of papaverine is more convincing than that for the xanthines This drug, at first used in doses which were much too small, had fallen into some disrepute until it was intensively investigated by Katz and co-workers. The studies of Elek and Katz[29] revealed that papaverine has the following primary direct actions on the dog's heart. (*1*) It decreases or eliminates ventricular premature beats induced on either a fixed part or different parts of the cardiac cycle (*2*) It enhances the difficulty of producing or maintaining auricular fibrillation by means of a faradic current. (*3*) It prolongs the refractory period of the myocardium In large doses, this drug depresses auriculoventricular and intraventricular conductivity leading to auriculoventricular and intraventricular block. In toxic or nearly toxic doses it causes active ectopic ventricular rhythms, including premature systoles, par-

oxysmal tachycardia, flutter, or fibrillation; and cardiac standstill or complete auriculoventricular block.

Papaverine is a useful drug in the anginal syndrome, having beneficial effects in about 75 per cent of the cases when used in doses of 1½ grains (0 1 Gm) four times a day. It apparently acts both as a sedative and as a coronary dilator. It also helps to prevent or lessen the occurrence of premature systoles or certain types of rapid heart action.

The changes in conductivity when large doses are used have been mentioned In a recent study of the drug's effect on ectopic beats in the dog, it was found that: (*1*) in small doses it has some temporary ectopic suppressor effect, (*2*) in larger doses, it has some stimulating effect on ectopic impulse which may go on to ventricular tachycardia. There is therefore some reason to fear its action in myocardial infarction, especially in the presence of ventricular tachycardia.

Two deaths after the intravenous injection of papaverine have been reported.[96]

Opinion about the therapeutic effect of papaverine, like that about most other drugs for the treatment of angina pectoris, is not unanimous Nevertheless, I have found it to be effective in many patients, and at the moment am prescribing, when necessary, a long-acting nitrite before meals and papaverine combined with phenobarbital after meals. On this regimen, the majority of patients feel comfortable and need less nitroglycerin than formerly.

DIOXYLINE PHOSPHATE (PAPAVERIL) This synthetic drug is somewhat similar to papaverine, it dilates the coronary vessels in dogs and in albino mice Encouraging reports[67, 99] and discouraging ones[37, 89, 95] are about equally divided. The dose is 3 grains (0 2 Gm.), three or four times a day, before meals and at bedtime.

KHELLIN (AMMI VISNAGA; VISAMMIN) This drug has aroused some interest since its introduction by Anrep in Cairo. The reports on its clinical effect have been voluminous but confused. There seems to be little doubt that this preparation acts potently to increase coronary flow in experimental animals.[14, 33, 52, 104] It probably has a direct effect on the coronary vessels, and there is some reason to believe that it also has a direct effect on the myocardium.

Favorable results with khellin therapy in man have been reported by many investigators.[14, 24, 65, 71, 74, 89] Others have been unimpressed with its effect on angina pectoris or the coronary circulation[44, 49, 55, 91, 105] The drug may be given by mouth, in enteric or sugar-coated tablets, in a dosage of 50 to 300 mg. per day, or intramuscularly in doses of 100 mg. Good results have been reported with this latter mode of administration[19, 64]

The most important factor limiting the use of khellin orally has been the high incidence of toxic reactions—nausea, vertigo, vomiting, insomnia, anorexia, and diarrhea—which are not prevented by enteric coating.[7] Troublesome side effects were noted in as high as 60[2] and 62[21] per cent of patients. Intramuscular administration seems to reduce the number of these complications[19]

Efforts are being made to modify and purify khellin, and these products merit further study. Nokhel, a soluble solution, seems to be inferior to natural khellin.[8] A pure crystalline drug has been described as giving generally good results in doses of 200 mg daily.[98] Improvement in 17 of 19 patients has been reported, untoward reactions being minimal when 50 to 100 mg. were used each day; a combination of 50 mg. khellin (crystalline), 15 mg. phenobarbital, and 10 mg. extract of belladonna is recommended in this report.[71]

Use of khellin in disturbances of sinoauricular, auriculoventricular, or intraventricular conduction, in postinfarctive states, and in cardiac insufficiency is inadvisable.[76] After a long trial, I have given up the use of khellin and am awaiting further reports.

HEPARIN Much has been written about the possible beneficial effect of injections of heparin in angina pectoris.[30, 42] Its proponents are uncertain about the drug's exact mode of action, but some feel that it is related to heparin's "clearing action" on the blood lipids Generally speaking, recent reports have not been encouraging[20, 43, 53, 64, 76, 86] I have used the drug as prescribed by its advocates—25 to 100 mg intravenously once a week—in 20 patients, but am not persuaded of its effectiveness

ATROPINE Abundant evidence points to the effectiveness of atropine in increasing coronary flow in experimental animals,[101 108 111] and its use has been advocated in the treatment of early human infarction [41] Rein[41] states: "Failure of relaxation from vagal tone can result in actual vasoconstriction when there is lack of equilibrium between the supply of blood for the myocardium and the demand " Atropine is of some value in preventing postprandial angina; if used for this purpose, it should be given in customary doses before meals. The combination of aminophylline and atropine is said to be more effective than either alone [55]

QUINIDINE It is still not completely certain whether this drug enhances coronary flow [13 28 56 58 113] Clinically, it is of some value in suppressing anginal attacks which are associated with premature beats and other ectopic rhythms [79] Some observers have found that patients with angina pectoris experience an increase in comfort and exercise tolerance when taking 5 grains (0 3 Gm) three or four times a day, quinine is almost as effective This beneficial action is ascribed, at least in part, to vasodilatation [87]

VITAMIN E AND TOCOPHEROLS These have been used extensively in the treatment of coronary disease Although some patients claim that the tocopherols have a mild euphoric effect, there is good evidence that they have no effect on anginal pain.[60 64 85] In a long trial period in over 100 of my patients, the tocopherols were of no more help than placebos.

OTHER MEASURES

ABDOMINAL SUPPORT

Some 20 years ago, it was reported that a special abdominal belt helped some patients with angina pectoris,[51] a later report stated that about 15 per cent of their patients had benefited from an abdominal support, and that it was possible to predict those who would be aided on the basis of changes in the ballistocardiogram.[17] Others have found that in 20 per cent of patients with abnormal ballistocardiographic changes (Grades 2 to 4), use of the elastic Brown-Spencer girdle improved the tracing.[26] In my experience, this is about the percentage of patients with angina pectoris who will claim benefit from abdominal support. The improvement, which is probably the result of increased venous return to the heart, can often be obtained by using a simple binder improvised from a wide elastic bandage.

ROENTGEN THERAPY

Irradiation directed to the heart itself has been tried in the past, and seems to have been generally abandoned Similar treatment directed to the cervicodorsal area, in an effort to affect the sympathetic chain, has not been promising [49 61] Deep irradiation of the adrenal glands was suggested by Raab,[81] 28 of 38 patients in one series improved [83a] Other observers were not encouraged, getting the same results with sham therapy as with irradiation,[49] however, they did not use the dosage advocated by Raab.

SHORT WAVE DIATHERMY

This has been extensively employed in Europe, with the rationale that direct heating of the heart tends to improve the coronary circulation. Summing up the literature and discussing the technic and hazards of the method, Bierman[5] concluded "It is difficult to prove any special value to the use of short wave current in the treatment of angina pectoris because spontaneous remissions occur in this disease, and because rest and other measures are applied concurrently."

DIURETIC TREATMENT

An "antiretentional" diet, with occasional injections of a mercurial and administration of aminophylline, has been advised in angina [53] It has also been reported that 1 ml. of Mercuhydrin, intramuscularly, every other day was beneficial to 5 patients with severe angina decubitus [75] I have no experience with these methods as routine therapy, but feel sure that patients with early heart failure and even slight water retention are helped by salt restriction and dehydrating measures

NICOTINIC ACID

Infusions of 0.05 per cent nicotinic acid have been reported as giving favorable results in the treatment of angina,[73] others have not been able to confirm these claims.[43, 104]

RADIOACTIVE IODINE

Total removal of the thyroid gland for the treatment of congestive heart failure or angina pectoris was proposed in 1932 and 1933, and two large series were reported from Boston, where this treatment was suggested.[11, 59] Thereafter, surgical thyroidectomy was the subject of some investigation, but recently interest has been focused on medical methods of inducing hypothyroidism

With the advent of antithyroid compounds (thiouracil, methylthiouracil, propylthiouracil), and more recently of radioactive iodine (I^{131}), these means of suppressing the thyroid have been proposed for angina pectoris[5, 6, 40, 47, 61, 97, 107] The antithyroid compounds have been largely superseded by I^{131}.[80] Results from a total oral dose of 25.5 to 176 millicuries of I^{131} have been reported as excellent in about 33 per cent of the patients, and "worthwhile" in another 33 per cent. Clinical improvement coincided with the onset of hypothyroidism. Additional benefits are improved emotional stability in irritable patients, and improvement of congestive heart failure[9] In general, patients did not complain of discomfort, even when the basal metabolic rate dropped to −25 per cent, an occasional patient required thyroid extract. A transient thyroiditis occurred in about 66 per cent of the patients

The criteria for the selection of patients are[9] (*1*) severe but not progressive angina, (*2*) normal or only slightly elevated blood pressure; (*3*) basal metabolic rate not lower than −10 per cent. Results of treatment of 574 patients in 40 clinics, followed for more than a year after the end of treatment, were good or excellent in 441 patients (76 per cent)[10] The only patients treated were ones who were incapacitated or were unable to work despite all the treatment they had received

At the University Hospitals in Cleveland, 130 patients have been treated with I^{131}[85] The results were good or excellent in 70 per cent of the cases of angina and in 55 per cent of the patients with intractable heart failure The response seemed to be best in the patients in whom myxedema developed In euthyroid patients, treatment is started with a 6 week course of propylthiouracil, followed by a single dose of 35 to 40 millicuries of I^{131}, an attempt is made to have about 400 microcuries per gram of thyroid tissue retained

The reported results are promising, but the follow-up period is still too short for definite conclusions. At least theoretically, there would seem to be a risk that the increase in blood cholesterol in the myxedematous state would adversely affect atheromatous arteries Some workers believe that the fear of risk of atherosclerosis in myxedema has been exaggerated, while the blood cholesterol rose an average of 125 mg per 100 cc in a series of cases of induced hypothyroidism, none showed any evidence of increased coronary disease[12] In young patients with rheumatic heart disease who survived for 3 to 11 years after myxedema was induced by thyroidectomy, autopsy revealed minimal coronary atherosclerosis[11]

SURGICAL PROCEDURES AND USE OF DRUGS IN PATIENTS WITH CORONARY DISEASE

SURGICAL PROCEDURES

Obviously, surgery may become necessary in patients with coronary artery disease Elective surgery should be postponed, if possible, for 3 to 6 months after an acute infarction However, emergency surgery must sometimes be done earlier, in 1 of my patients, bilateral iliac vein ligation was probably lifesaving when phlebothrombosis with pulmonary emboli occurred on the tenth day after a major infarction Successful operation for a saddle embolus on the eleventh day and successful appendectomy on the sixth day[35a] have been reported, and in a patient of mine an appendectomy was successfully performed on the fifth day.

In general, surgery is fairly safe in patients with old infarction or angina pectoris, although it should never be undertaken lightly Among 257 patients with cardiac disease undergoing major operations, 4 3 per cent died[17a] In another series, there was an over-all (not cardiac) mortality of 8 6 per cent in patients with angina and of 8 1 per cent in patients with myocardial infarction,[49a] in still another series, the mortality was 6.3 and 7.2 per cent, respectively[4a] Of 17 patients with old myocardial infarction undergoing 30 operations 3 died, none of 15 patients with

TABLE 27 SURGICAL PROCEDURES FOR CORONARY DISEASE

- Revascularization
  - Use of pericardium to form new collateral channels
    - Attachment of pericardial surface to omentum, muscle, or lung
    - Induction of inflammatory reaction by introducing foreign substances, such as talc (poudrage)
    - De-epicardialization combined with poudrage
  - Ligation of coronary sinus
  - Production of direct anastomoses
    - Resection of occluded artery
    - Transplantation of artery directly into myocardium
    - Arterialization of coronary sinus
- Neurosurgery to block afferent pathways
  - Chemical nerve block
  - Posterior rhizotomy
  - [illegible] ganglionectomy
  - [illegible]rectomy
- Other procedures

[illegible] in the experimental animal.[11] [illegible] stimulation of [illegible] collaterals prob- [illegible] protection against [illegible] the normal dog heart; the [illegible] channels in supplying blood to the pericardium when pericardial adhesions are produced surgically is minimal or nonexistent.[14, 19] They conclude:

> In brief, demonstration of the larger anastomatic channels produced as a consequence of the operative procedure has not received adequate attention. Nor are there any convincing blood flow studies which demonstrate that any therapeutic surgical operation leads to a sustained increase in arterial blood flow in a heart with prior coronary narrowings or occlusions. Caution must be observed in applying the results of experiments on the normal dog heart to the diseased atherosclerotic human heart with its established narrowings, occlusions and rich network of compensating intercoronary anastomoses.

The nonspecific effect of any operation on the heart must also be evaluated. It has been repeatedly found that ligation of the anterior descending artery in the normal dog causes the death of 75 per cent of the animals, and almost any proposed surgical procedure has resulted in "protection" against this mortality. Harken and associates[20] conclude:

> It is a remarkable fact that approximately 75 per cent of animals have survived ligation of the anterior descending coronary artery regardless of which of the diverse "protective" procedures was employed. . . . The inescapable conclusions that are derived from these reports is that most of the operations are successful in a substantial number of instances and possibly, for the most part, *not* for the reasons put forward. It is conceivable that intrinsic collateral channels, as opposed to an external collateral coronary supply, have been opened. The significant increase in coronary back flow reported by Beck following a "sham operation" in which he went through all steps of his second method without permitting actual reversal of circulation to occur supports this view.

REVASCULARIZATION

USE OF PERICARDIUM TO FORM NEW COLLATERAL CHANNELS

ATTACHMENT OF PERICARDIAL SURFACE TO OTHER TISSUES *Claude* Beck, the pioneer in this type of operation, *indeed the pioneer in the direct surgical approach to the heart*, and his associates began *the search for surgical methods of improving* the cardiac blood supply in 1932; their first report was made in *1935.*[9] *On the* basis of Beck's observations, O'Shaughnessy,[45] did an anterolateral thoracotomy and applied a pedicle graft of the great *omentum* to the heart. Beck has used muscle instead of omentum. Others have modified this proce-

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angina pectoris undergoing 21 operations died.[60b]

SHOCK TREATMENT

This is not advisable in patients suffering from coronary disease, but it may be used if the psychiatric indications are urgent.[50a]

ANESTHESIA

In a discussion[26a] of the problem of anesthesia in patients with coronary disease, it is urged that: (*1*) the patient receive assurance with regard to the anesthetist's knowledge and competence; (*2*) adequate preoperative sedation be used, (*3*) anesthesia be induced smoothly; (*4*) blood pressure be maintained: and (*5*) adequate amounts of oxygen be administered.

[illegible]

USE OF DRUGS

Certain drugs should be avoided or used with great caution in the presence of chronic coronary disease. The most hazardous drug is pitressin, which induces considerable coronary vasoconstriction in dog preparations even when used in small doses. These results are in accord with those reported on surviving human hearts, rabbit hearts, human strips, and isolated ox hearts[18 43 50 72] Since indications for the use of pitressin in man are few, it is safer not to use it at all Death or infarction has followed its use.[57 69 100]

Insulin may have a deleterious effect on the myocardium.[29] When it produces hypo- [illegible] should not be avoided in persons with coronary disease, but care must be exercised not to lower the blood sugar excessively.

Antabuse (tetraethylthiuramdisulfide) may induce drops in blood pressure and electrocardiographic changes even in presumably normal individuals,[62 63] it should be used with caution or avoided in those with coronary artery disease.

Hexamethonium salts, like all agents inducing hypotension, should be used with the greatest care in coronary disease There is evidence that it may impair coronary flow in both animals and man.[22 34]

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CHAPTER 18

Surgical Treatment of Coronary Disease

SEVERAL DECADES ago, neurosurgeons joined the internists in the therapeutic attack on angina pectoris More recently, other surgeons have enthusiastically joined in the struggle. Thoracic surgeons, emboldened by their successes with congenital and rheumatic heart disease, have devised increasingly ingenious and daring operative technics, and thereby, especially in their preliminary animal experiments, have often solved puzzling cardiac problems So far, they have been not completely fortunate in their therapeutic results in coronary disease, but the same may be said of their medical colleagues However, since the initial accomplishments have been striking enough to be encouraging, an attempt to record and weigh the achievements of surgical intervention is justified.

The natural history of any mode of treatment—surgical or medical—is the same Depending on the enthusiasm and persuasiveness of the proponent, the procedure enjoys a period of great success, often followed in turn by criticism, skepticism, and slow abandonment However, much has been learned even from some of those which have been discarded

The physician's attitude should be that of watchful and moderately optimistic waiting, in most patients with coronary disease, the course is generally favorable If he permits operative intervention, he should insist on a method the risks of which are no greater than those of inaction, nor can he allow himself to be deprived of good judgment by patients who are swayed by accounts in the popular or medical press

Surgical measures fall into three divisions (*1*) those aimed at relieving ischemia by revascularizing the heart, (*2*) those aimed at relieving pain by blocking afferent nerve pathways; and (*3*) those aimed at reducing the metabolic demands on the coronary circulation (Table 27).

The objective of most present investigation is to relieve myocardial ischemia by increasing cardiac vascularity The preliminary research has necessarily been largely confined to animal experiment; the pitfalls in transferring experimental results to man are emphasized by Blumgart and Paul.[10]

> Proof of the surgical augmentation of arterial blood supply to the myocardium has been beset with difficulties Experimental studies utilizing the dog encounter a different coronary arterial tree from that of man Large anastomoses between the left anterior descending and left circumflex and right coronary occur rather frequently in the dog thus rendering the effects of ligation of a single artery such as the left anterior descending in a series of experiments highly variable and difficult to interpret

They go on to point out the technical problems which complicate attempts to demonstrate a new, functional blood supply in experimental animals after operative procedures Capillary intercoronary anastomoses are normally present and similar communications often extend to neighboring structures, such as the aorta and pulmonary artery[22] While such fine connections do not protect the myocardium from infarction in sudden occlusion of a coronary artery, intercoronary anastomoses have been shown to be abundant and always present when coronary narrowing or occlusion has existed for a time These anastomoses prevent the catastrophic effects of

TABLE 27. SURGICAL PROCEDURES FOR CORONARY DISEASE

Revascularization
Use of pericardium to form new collateral channels
Attachment of pericardial surface to omentum, muscle, or lung
Induction of inflammatory reaction by introducing foreign substances, such as talc (poudrage)
De-epicardialization combined with poudrage
Ligation of coronary sinus
Production of direct anastomoses
Resection of occluded artery
Transplanation of artery directly into myocardium
Arterialization of coronary sinus
Neurosurgery to block afferent pathways
Chemical nerve block
Posterior rhizotomy
Cervicothoracic ganglionectomy
Pericoronary neurectomy
Other procedures

sudden occlusion in the experimental animal.[31] As studies have shown, the stimulation of such functional intercoronary collaterals probably explains the prolonged protection against coronary ligation in the normal dog heart; the role played by vascular channels in supplying blood to the pericardium when pericardial adhesions are produced surgically is minimal or nonexistent.[14, 19] They conclude:

> In brief, demonstration of the larger anastomatic channels produced as a consequence of the operative procedure has not received adequate attention Nor are there any convincing blood flow studies which demonstrate that any therapeutic surgical operation leads to a sustained increase in arterial blood flow in a heart with prior coronary narrowings or occlusions. Caution must be observed in applying the results of experiments on the normal dog heart to the diseased atherosclerotic human heart with its established narrowings, occlusions and rich network of compensating intercoronary anastomoses

The nonspecific effect of any operation on the heart must also be evaluated. It has been repeatedly found that ligation of the anterior descending artery in the normal dog causes the death of 75 per cent of the animals, and almost any proposed surgical procedure has resulted in "protection" against this mortality. Harken and associates[28] conclude:

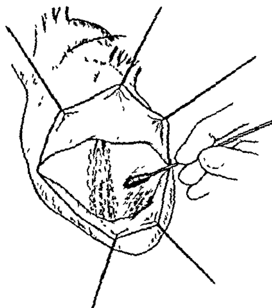
> It is a remarkable fact that approximately 75 per cent of animals have survived ligation of the anterior descending coronary artery regardless of which of the diverse "protective" procedures was employed . . . The inescapable conclusions that are derived from these reports is that most of the operations are successful in a substantial number of instances and possibly, for the most part, not for the reasons put forward It is conceivable that intrinsic collateral channels, as opposed to an external collateral coronary supply, have been opened The significant increase in coronary back flow reported by Beck following a "sham operation" in which he went through all steps of his second method without permitting actual reversal of circulation to occur supports this view

REVASCULARIZATION

USE OF PERICARDIUM TO FORM NEW COLLATERAL CHANNELS

ATTACHMENT OF PERICARDIAL SURFACE TO OTHER TISSUES Claude Beck, the pioneer in this type of operation, indeed the pioneer in the direct surgical approach to the heart, and his associates began the search for surgical methods of improving the cardiac blood supply in 1932; their first report was made in 1935.[9] On the basis of Beck's observations, O'Shaughnessy,[43] did an anterolateral thoracotomy and applied a pedicle graft of the great omentum to the heart. *Beck has used muscle instead of* omentum. Others have modified this proce-

dure. Mason[41] reported on 30 patients in 1951: 11 of the 30 did not survive the first month; in 3, the angina was not relieved, 10 seemed to be benefited, and in 6 the relief was questionable. Even bearing in mind that Mason included patients whose state was rather hopeless, the results are not encouraging Lezius,[39] and Carter and associates,[35] have used the lungs as a source of extracardiac blood. Key and co-workers[91] have applied the raw surface of a split segment of isolated jejunum, stripped of mucosa but attached by its pedicle, to the heart surface of experimental animals, and report that this affords a high degree of protection against the ill effects of subsequent coronary artery ligation Generally speaking, this operation, as a solitary procedure, has been discarded It still survives as part of other operations



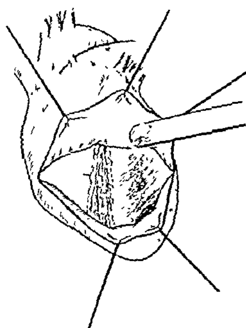


FIG 100 Decortication by phenol and poudrage (Left) The open pericardium The left ventricle is swabbed, front and back, with phenol, care being taken to avoid the coronary vessels (Right) The application of talc at the same operation (Courtesy of Dr A Bakst)

POUDRAGE (CARDIOPERICARDIOPEXY, INSTILLATION OF POWDERED TALC OR ASBESTOS INTO PERICARDIAL CAVITY) (Figs 100, 101) The use of pericardium as a source of collateral circulation was proposed in 1932 [4] In 1935 Robertson[90] reported the induction of an artificial pericarditis. The next year O'Shaughnessy[15] used Aleuronat paste to produce a body reaction in the pericardial cavity, Beck used powdered beef bone This type of operation received its first real impetus in 1939, when Thompson[58] reported the use of talc. His enthusiasm for this method has continued and a large number of patients have been treated successfully.[59] In the experience of these workers, instillation of sterile anhydrous magnesium silicate (U.S.P talc) into the pericardial sac is a satisfactory method of producing an adhesion pericarditis, a pronounced hyperemia occurs within a few hours and persists for 2 or 3 weeks This hyperemia is said to open up anastomotic channels already present and to stimulate the formation of new ones The inflammatory myocardial reaction may cause formation of new intracardiac, as well as extracardiac, vessels There seems to be no danger of a constrictive pericarditis as a late result The operation in Thompson's hands takes about 20 minutes

TECHNIC An incision 3 inches long is made over the left fifth costal cartilage, the medial end being at the costosternal junction

After careful dissection, the pericardial sac is aspirated through a small incision and 5 cc. of 2 per cent novocaine are dropped onto the epicardium to prevent subsequent fibrillation. The novocaine solution is aspirated after 5 minutes, about 2 drams of sterile talc are then applied over the anterior surface and inferior and left borders of the heart, and the incision is closed *Cyclopropane anesthesia, with large* quantities of oxygen, is used

There is usually a pronounced reaction, with fever and inflammatory involvement, not serious, of the left lower lobe of the lung, the adjacent pleura, and the mediastinum. A friction rub is heard for a long time, and the ECG shows the changes of an acute pericarditis. Pain on moving the left arm and shoulder is frequent, and may persist for some time postoperatively; it is due to the involvement of the pectoral muscles at the operation

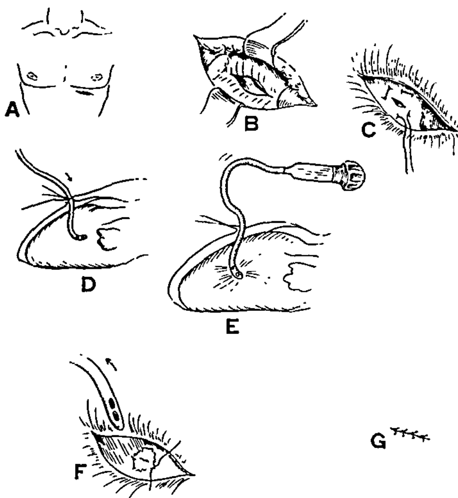


FIG 101 Poudrage, Bailey's procedure A, Incision 4 to 7 cm long is made over left fifth costal cartilage B, Cartilage is resected and perichondrial bed is incised *C, Extrapleural portion of pericardium is exposed,* care being taken not to enter pleura (free pericardial space); purse-string suture is applied in pericardial substance and a small stab wound is made within its confines D, Soft rubber (urethral) catheter of adequate size is inserted through stab wound deeply into pericardial sac E, Suspension of irritant in procaine is injected F, *Catheter is withdrawn and pericardial wound is closed* by constriction of the purse string G, Skin is closed by simple or interrupted mattress sutures (From Bailey Surgery of the Heart, 1955 Courtesy of Lea & Febiger)

Schildt, Stanton, and Beck,[51] after testing *28 chemical substances, concluded that powdered* asbestos, also a silicate, was superior to talc. Bailey[3] concurs, and uses asbestos routinely when doing this type of operation His procedure is:

TECHNIC After induction of general anesthesia, a 3 cm. section of the left fifth costal cartilage is removed through a 5 cm incision. The pericardium is incised through a small cut without opening the pleura, any fluid present is aspirated, and 4 Gm. of powdered asbestos, previously mixed with 30 ml. of 2 per cent procaine solution, is injected with a bulb syringe through a catheter, the tip of which has been placed within the pericardium behind the heart. Closure is made without drainage. Morphine and oxygen are administered for 2 to 3 days to combat the considerable pericardial pain.

Fever may last for 10 days. Pericardial effusion is not a postoperative problem. According to Bailey, the patient is free of pericardial pain within 3 days, and no further anginal pain may ever be experienced. When it persists, it is usually milder than before treatment. Bakst[4] believes that the skin incision should be small and that the dry powder should be applied rather than blown in He reports that arrhythmias occur more commonly when the powder is insufflated Dack and Gorelick,[18] using the talc method in 36 patients, had an operative mortality of 5.5 per cent (2 patients) In more than three-fourths of those operated upon, improvement was good or excellent. Boone and Hubbell[13] report the use of 5 per cent monoethanolamine oleate solution as an irritating agent to produce an adhesive pericarditis in experimental animals Blumgart and associates,[11] basing their opinion on experiments done on pigs, cast doubt on the efficacy of pericardial adhesions They found collateral vessels in the vicinity of pericardial adhesions, but in no instance did their injection mass traverse these adhesions

Bailey[4] believes that the Thompson procedure is not a wholly satisfactory method of revascularization, and feels that in general the attempts at cardiac revascularization by intrapericardial irritants or surface application of vascular grafts are probably of relatively small fundamental value to the patient However, these procedures undeniably result in palliation of pain, and perhaps also provide enough additional blood to the superficial layers of the ventricles to offer protection against the development of "dry" areas in the myocardium and so avoid the onset of fatal ventricular fibrillation Time is also gained for the possible development of additional auxiliary sources of myocardial nutrition. "Since the ischemic myocardium presents a constant need, the arterioluminal and other primitive mechanisms may become directly continuous with the intercoronary collaterals, overdeveloped and brought more fully into utilization." Thompson[57] has now accumulated a large series of cardiopexy operations. The operative mortality (postoperative and hospital deaths) in 180 operations was 10 per cent. Some of these deaths he considers not to be related to the surgery, being due to rupture of an unsuspected abdominal aortic aneurysm or to diabetic coma; they are nevertheless included in the mortality statistics In 90 per cent of his series there was an improvement of 50 to 100 per cent (good to excellent), in 40 per cent the improvement was better than 75 per cent. Most of the patients are gainfully employed. Those patients who subsequently died lived an average of 9½ years after the onset of symptoms, which he believes is about 5 years longer than they would have lived under medical treatment alone

The Beck I operation, now used almost exclusively by Beck and colleagues, consists of the instillation of asbestos, cardiac abrasion, partial coronary sinus occlusion, and grafting of pericardium and mediastinal fat. They firmly believe that this procedure adds little to the risk of operation, compared to simple asbestos instillation, even in poor-risk "salvage" patients. If difficulties occur, they are "the effects of anesthesia plus thoracotomy and not so much by what is done to the heart"[8] Beck feels that the intercoronary anastomoses resulting from the Beck I operation are almost as profuse as those from the Beck II operation, and the risk is considerably smaller

Leighninger[34] sums up the current attitude of the Beck group as follows:

> Our attention has recently been returning to Dr Beck's original concept of the "trigger" with more and more emphasis We have evidence that when cyanotic myocardium is in contact with oxygenated myocardium certain measurable electric currents are set up which are capable of destroying the coordinated mechanism of the heart beat This is true whether it be an island of blue muscle in contact with pink muscle, or an island of pink muscle in contact with blue muscle

The importance of these currents is becoming more clear. Yater, in his analysis of 950 deaths from coronary artery disease, has shown that in about 90% of these hearts there was not considerable destruction of myocardium. The majority of these deaths were due to destruction of the mechanism of the heart beat, rather than due to heart failure due to a "worn out" heart from excessive muscle damage Most of these hearts were hearts that, under slightly altered conditions, probably had the capacity for continued function for a period of time, probably in terms of months or years We think that the electric currents from "trigger" areas were responsible for the majority of these deaths We also know that a few cubic centimeters of blood per minute to an area of myocardium which is in need of blood can markedly alter the possible outcome of such a heart We think that intercoronary communications can supply these small quantities of blood to such areas by providing an even distribution of blood to the myocardium, even though no new blood supply has been added to the heart These small quantities of blood can alter the electric currents so that the mechanism of the heart beat is not destroyed We know that operation can stimulate the production of intercoronary communications We also know that coronary atery occlusion also stimulates the production of intercoronary communications The question for many patients, then, is whether or not intercoronaries can develop fast enough to keep up with the progress of his disease. The 200 to 400 thousand deaths per year from coronary artery disease stands as evidence that this development for many people is not fast enough We do feel that operation can provide sufficient intercoronaries to make a significant difference to many of these people.

We are aware that operation can not alter the progress of the disease within the coronary arteries nor can it undo the damage already in the myocardium, but we do feel that it can help prevent or protect the heart from the effect of these currents which can produce ventricular fibrillation In the course of so doing it has also brought about significant relief of pain and returned to useful occupations about 80 to 85 per cent of the patients operated

DE-EPICARDIALIZATION Harken and associates[26] advocate the application of phenol to the pericardium in order "to remove the barrier to the ingrowth of vascular collateral circulation." Harken also applies the lingula of the lung to the denuded myocardium as a highly vascular source of new blood supply. The operation consists therefore of: (*1*) de-epicardialization with 95 per cent phenol, (*2*) poudrage, and (*3*) pneumonopexy. In both man and experimental animals, there is less operative arrhythmia, and improved results have been found. None of 18 patients who have undergone the operation have died, and the relief from pain has often been dramatic

LIGATION OF CORONARY SINUS (Fig. 102)

In 1937, on the basis of animal experiments, Gross and colleagues[24] proposed that the induction of venous congestion might improve the coronary circulation, and Fauteux[21] was sufficiently encouraged by the results of his animal experiments to use this operation in patients. Their theories are largely based on the following, generally accepted assumptions

(*1*) The coronary sinus receives from 40 to 70 per cent of the inflow of the left coronary artery. The right ventricle is supplied chiefly by the right coronary artery and is drained in large part by the accessory veins. However, the left coronary artery supplies some part of the right ventricle, and part of the right coronary inflow is drained by the coronary sinus.

(*2*) An accessory drainage system, the thebesian vessels, is present in both auricles and ventricles. They communicate with each other, with the cardiac cavities, and with the cardiac veins, but their only connection with the arterial system is through the capillaries.

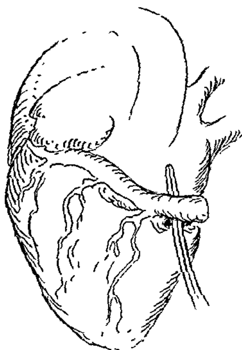
(*3*) The coronary arteries communicate with the cardiac chambers through the arterioluminal and arteriosinusoidal systems, both of which have networks with interarterial anastomotic vessels. The capillary bed is in direct communication with all three systems, and with the veins which connect with each other and with the thebesian network

(*4*) The inflow or outflow systems have no valves Flow depends on pressure gradients, which in turn depend on such factors as pressure head, vessel size, position of vessel in the myocardium, and on systolic and diastolic pressures within the myocardium and the cardiac cavities.[18]

In 1946, Fauteux[21] reported ligation of the great coronary vein in 10 patients; 7 of them were alive and improved 3 to 5 years later. Other investigators, working with animals, have had no success with this method and challenge its theoretic validity[22, 39, 50, 60] They

point out that presumably, with the overdevelopment of other normal venous drainage pathways, the induced coronary sinus hypertension will in time become reduced, with loss of the beneficial effect of coronary ligation.

The pioneer work of Fauteux and of Gross and associates was important in showing that the coronary sinus could be sacrificed without great harm. In the United States, coronary sinus ligation alone is seldom performed, but it may be used in combination with other procedures Beck combines it with epicardial abrasion and intrapericardial instillation of asbestos (Beck I procedure) for patients considered unsuitable for the more formidable Beck II procedure, which itself includes a partial occlusion of the coronary sinus.



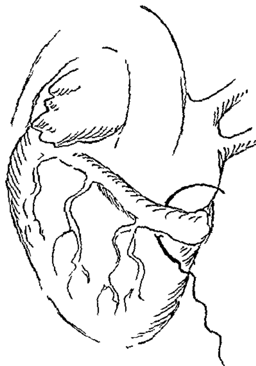


FIG 102 Simple ligation of coronary sinus (Left) Passage of pair of dissecting forceps under sinus, after dissecting fat in which it is imbedded on either side (Right) Passage of threaded large curved needle under sinus, dark venous bleeding indicates deep tearing of sinus or a tributary and requires repassage at a deeper level bleeding of arterial blood may indicate entrance into left atrium but is of no importance and does not necessitate repassage of needle (From Bailey: Surgery of the Heart, 1955 Courtesy of Lea & Febiger)

PRODUCTION OF DIRECT ANASTOMOSES

RESECTION OF OCCLUDED ARTERY

Murray[42] has proposed the most direct surgical approach possible He has resected the narrowed portion of the artery and replaced it by a vascular graft in 5 patients. The distal portion of the artery was perfused during the operation by way of a branch, to prevent infarction of the involved muscle Such a surgical procedure would seem, at least theoretically, to be correct for the occasional solitary, sharply localized atheroma This is sometimes the case in young people, but how certain can the clinician be? Perhaps it is the operation for the rare case in which the surgeon, exploring the heart with a choice of several procedures, finds the morbid changes exactly suitable. Murray[42] himself does not believe that it should be advocated as a clinical procedure, for the present at least

DIRECT TRANSPLANTATION OF ARTERY INTO MYOCARDIUM (Fig 103)

Vineberg,[81] working first with dogs, devised an operation to increase the heart's blood supply by transplanting the cut free end of an internal mammary artery to a previously prepared tunnel in the wall of the left ventricle He is

convinced that successful revascularization is accomplished, and in 1953 reported on 9 patients treated by this method; 3 patients died, of the survivors, 3 were completely relieved of their pain Bailey[1] has found that revascularization in animals subjected to the Vineberg technic seems to be limited to the anterior portion of the left ventricle and to the anterior half of the interventricular septum (an area commonly involved in human infarction), and has noted a high percentage of postoperative thromboses in his animals In Murray's[44] experience, the artery has become occluded in a high proportion of cases. Bakst and associates[6] have found that the lumens of the implanted vessels in animals who lived for 6 months after the Vineberg procedure were 95 per cent obliterated by severe intimal proliferation. They concluded that the operation did not materially increase the collateral circulation.

The results of the Vineberg procedure have not been encouraging so far, but the idea is an intriguing one. Vineberg himself feels that the implantation is much more likely to be successful if the ventricular wall is already ischemic and in need of extra circulation. Future experimental studies, based on these conditions, will perhaps demonstrate whether this procedure has merit.

ARTERIALIZATION OF CORONARY SINUS (Figs. 104, 105) Pratt,[47] as early as 1898, proposed that nourishment of the myocardium might be increased by retrograde flow into the coronary sinus. Roberts and associates,[49] working with heparinized dogs, connected an artery to the coronary sinus by means of a glass cannula. *Smith and coworkers*[53] ligated the circumflex artery in dogs, and found that the mortality rate was reduced from 70 per cent to 0 when the coronary sinus was successfully arterialized Eckstein and Leighninger[19] have had similar good results in dogs; they state: "It is likely . . . that the human being who is chronically disabled after myocardial infarction has not a deficiency in collateral development but rather a lack of adequate collateral perfusion due to disease in the remaining coronary arteries." Hahn and colleagues[25] showed that blood from the venous side can traverse the capillary bed and emerge from the arterial side. Some of their specimens showed communications between arteries and veins without the interposition of a capillary bed Other workers feel that

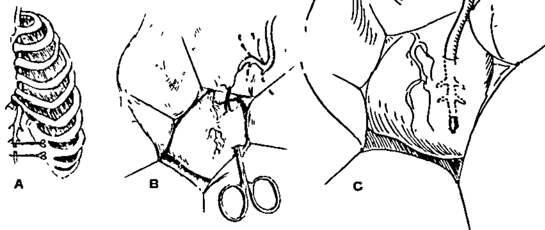


FIG 103 Vineberg procedure A, Left internal mammary artery is divided at level of sixth intercostal space and is mobilized up to level of the fourth B, Shallow tunnel 3 to 4 cm long is made within thickness of anterior wall of left ventricle, using a pair of fine curved mosquito forceps, intercostal stumps are reamputated to cause them to bleed freely C, Artery is drawn into myocardial tunnel and terminal ligature is tied to suture placed about ventricular stab wound (From Bailey [3])

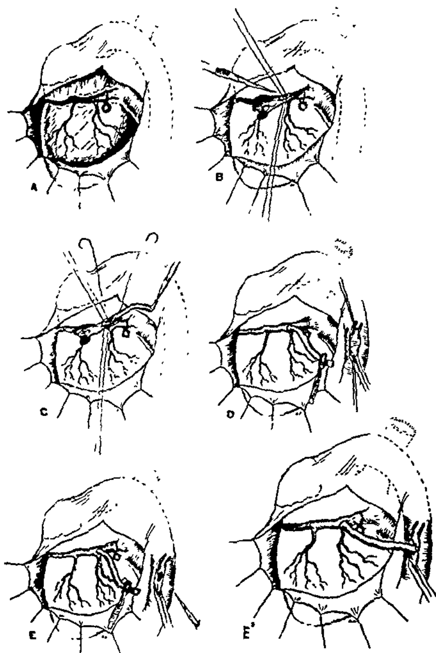
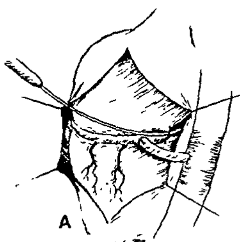


Fig 104 Arterialization of coronary sinus, Beck II procedure first stage A, Coronary sinus is encircled close to its ostium with a double suture of nylon; this is not tied but rolled up into a little "bale" which is "bound" with a fine arterial suture and then is secured to pericardium or diaphragm at a convenient place. B, Two traction sutures are placed fully into lumen of coronary sinus (indicated by venous bleeding from stitch holes); part of sinus wall is excluded, using special bull-dog clamp, sinus is incised longitudinally between the two sutures as slight traction is made upon them C, Using a suitable venous or arterial autograft, an end-to-side anastomosis is made to opening of sinus, an everting mattress or simple running suture technic may be used D, After sinus anastomosis has been proved secured, graft is filled with heparin solution and clamped terminally while a portion of contiguous wall of descending aorta is excluded with a special (Beck) aortic clamp E, E', Circular opening of 4 mm diameter is made in excluded portion of aortic wall, using a simple hand held bistuory blade, or preferably, a specially designed punch (From Bailey [3])

this procedure does not accomplish myocardial revascularization because of the existence of intramural communications between tributaries of the coronary sinus and other heart veins.[80, 82] These channels can grow larger and might then function as a complete run-off of all the extra arterial blood provided by the operation. However, Bailey and asso-



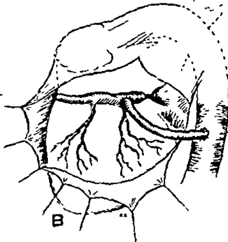
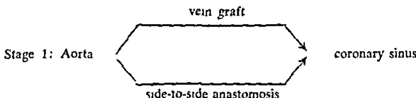


FIG 105 Beck II procedure, second stage A, Probe of measured size, usually 2 mm in diameter, is laid upon surface of coronary sinus near its terminus and the two encircling nylon sutures are successively tied down upon it B, After ligature is tight, probe is withdrawn, re-establishing a 2 mm luminal diameter After this, t major portion of the arterial blood from the graft m flow in retrograde fashion throughout the ramificatio of the coronary sinus system of veins

ciates[2] present their own laboratory investigations and those of others in support of its soundness

To Claude Beck of Cleveland goes the credit for adapting this operation to man. He devised an ingenious two stage procedure:



Stage 2 Incomplete ligation of the coronary sinus.

This method is designed to replace the lost arterial blood flow by reversing the flow through the coronary veins which end in the coronary sinus.

In Stage 1, an anastomosis is made between the aorta and the coronary sinus, a previously prepared vein graft being laid between openings made in each of these vessels. A recent modification accomplishes a direct side-to-s anastomosis when possible without vein gra with this method, *thrombosis is said to be l* of a hazard. The incision in the aorta must fairly large (4 to 6 mm. in diameter) to p vent thrombosis of the graft, especially in Beck II procedure.

In stage 2, done 3 to 6 weeks later, when anastomosis has healed, the coronary sinus partially (not completely) obliterated, a rel tively minor operation. A probe 2 mm. in d ameter is placed firmly on the sinus and ligature (placed but not tied in stage 1) is tie tightly around the probe and compressed sinu When the probe is removed, the caliber of th sinus will presumably be about 2 mm i diameter The two-stage technic is necessar because the ostium of the coronary sinus mu *be left open at the beginning. If the venou* radicles have not become adjusted to a highe intraluminal pressure, myocardial congestio and thrombosis of the graft are inevitable Were retrograde flow to occur suddenly, th myocardial venous system would be unabl

to tolerate the large blood flow necessary to retain potency.

The beneficial effects of arterialization of the coronary sinus are said to result from (*1*) Production of hypertension in the coronary sinus. (*2*) Overdevelopment of intercoronary arterial communications, producing a network through which arterial blood from any source could, theoretically, reach any portion of the myocardium; localized infarction would therefore be unlikely, nor would ventricular fibrillation due to "trigger" effect of areas of localized ischemia ("dry areas") be likely to occur. (*3*) Development of extracardiac communicating vessels, the newly developed mediastinal and pericardial vascularity, usually of high degree. Bailey[3] considers this an important, perhaps the most important, factor in increasing the cardiac blood supply.

The many drawbacks of the Beck II operation are listed frankly by Bailey.[3] The two-stage operation is time-consuming and costly. If the connection between aorta and coronary sinus is too small it will be occluded by clot, if too large, it constitutes an arteriovenous fistula and is therefore a burden on an impaired circulatory apparatus For the sake of safety, the coronary sinus must not be occluded completely in stage 2; on the other hand, the ligature may tighten itself and thereby occlude the orifice completely, or the flow through the sinus may become reestablished. In animals, retrograde flow of arterialized sinus blood is not maintained beyond 4 months, in man, it probably is not maintained for longer than a year or two. He believes this time to be sufficient for intercoronary and extracoronary communications to become so well established as to last for a long time, perhaps for life. Then again, the general dilatation of the intramyocardial vascular pathways may transform the myocardium into a more spongy tissue, this may be a "cavernous" transformation, having the histologic appearance of corpus cavernosum (Fig 106) This myocardial deterioration, and it must be so regarded, cannot fail to impair the vigor of the heart as a pump, this in the face of the added work imposed by the presence of an arteriovenous fistula.



FIG. 106 E, Interfascicular space of left ventricle in a 54 year old patient with history of two myocardial infarctions and definite aneurysm formation who died 3 months after the second stage of a Beck II procedure, note pseudoangiomatous change with even greater dilatation of the vessels, death due to congestive heart failure, graft open (X 80) F, Section through coronary sinus, showing intimal proliferation and medial hypertrophy (X 80) Such changes have been described as "arterialization" of the vein, they probably represent degenerative changes due to the abnormally elevated intraluminal pressure, ultimately, the smaller tributaries of this vessel become obliterated completely by extension of these changes and/or thrombosis. (From Bailey.[3])

With all of these shortcomings, Bailey's results convince him that the operation is eminently worthwhile for relieving pain and for preventing future infarction and ventricular

fibrillation He reports on 53 patients on whom the Beck II technic was used There were 8 operative and 3 late deaths (operative mortality, 16 per cent). Graft thrombosis, which formerly occurred in about a third of the cases, is now becoming rarer because of technical improvements introduced by Beck. The patients in whom graft thrombosis occurred fared poorly, but the majority in whom it did not, have done well. Only 1 patient has residual anginal pain, 2 have needed graft ligation (after 16 and 19 months) because of large output heart failure. "The others have reported relatively tremendous improvement in their ability to work and undertake activities." The ECG often shows a deterioration which does not correlate with clinical improvement.

The Philadelphia group of surgeons, recognizing the technical difficulties of the Beck II operation, have required that the patient be under 55, "that he should not have had more than two previous myocardial infarctions, that at least 6 months should have elapsed since the last infarction, that his heart should not be enlarged (radiographically) more than 10 per cent beyond normal limits, and that he should show no signs either of left or right ventricular failure Special considerations such as calcification of the aorta, hypertension, or metabolic disease (diabetes, obesity, nephrosis) might well be contraindicative or deterrent to the performance of this type of surgery."

Intracardiac instillation of a silicate powder is suggested for patients whose condition is not good enough to meet these requirements. Procedures aimed at interrupting the sympathetic pathways are reserved for those patients in whom all revascularization procedures are contraindicated

I do not feel, after sober appraisal of arterialization of the coronary sinus, that I can recommend this operation There is little doubt that the condition of the heart muscle, as muscle, is impaired by the procedure, whether the added blood supply makes up for this is scarcely certain after so short a period, only about 5 years having elapsed since Beck's first patient had this operation Longer and more definite follow-up studies are needed before final judgment can be passed. It is noteworthy that since January, 1954, Beck has returned to the I procedure as the operation of choice. Bakst and Bailey,[55] in a 12 month follow-up study of their experimental animals, found the grafts occluded in most of the animals and conclude that "retroperfusion of the myocardial capillary bed could not be demonstrated in this group of animals."

NEUROSURGERY TO BLOCK AFFERENT PATHWAYS

The neurosurgical procedures are designed to relieve the pain of angina pectoris. They do not improve the coronary circulation except in so far as they reduce pain which in turn may diminish coronary flow. The results have been equivocal so far. Some of the operations are still giving good results; others have been discontinued either because they have been superseded or because the results have been unsatisfactory There remains enough promise of success to give point to the belief of some neurosurgeons that cardiac pain can be relieved in most cases by surgical means.

There are three possible points of neurosurgical attack (*1*) The vasomotor nerves, the aim is to prevent vasoconstrictor impulses to the coronary arteries (*2*) The motor accelerator nerves, the aim is to interrupt cardiopressor reflexes (*3*) The sensory nerves, the aim is to interrupt pain pathways

The primary objective of current procedures is to block pain impulses; the other procedures would be accomplished in passing, if at all A description of the innervation of the heart will be found in Chapter 7

CHEMICAL BLOCK OF AFFERENT PATHWAYS

This procedure was first proposed by Mandl[40] in 1925 and by Swetlow[55] in 1926 The most important application of this method is paravertebral block with procaine or alcohol Novocaine injection induces temporary, and in some cases prolonged, relief. Alcohol injection produces a much longer, occasionally permanent, block.

The usual method is to inject the blocking agent paravertebrally, as indicated in Figure 107. This may be confined to the left side, but bilateral injection is sometimes required. The stellate ganglion may or may not be injected. In one series of 45 patients, relief was marked in 77.5 per cent[35] Alcohol injection in 22 pa-

tients resulted in complete relief for 7, partial relief for 9, and failure for 6.[10]

White and Bland[62] considered this method *the least dangerous one for poor-risk patients* Nevertheless it is not free of certain drawbacks and hazards: (*1*) Even when performed most skillfully, the procedure fails to control pain in 10 per cent[62] (*2*) The injection is carried out without anesthesia in order to observe the appearance of a Horner's syndrome and a hot, dry hand (*3*) The spinal cord may be injured if alcohol penetrates the subarachnoid space,[27] 3 cases of myelitis have been observed to follow this procedure[62] (*4*) There is danger of pulmonary puncture, pneumothorax, and pneumonia[40] (*5*) Several deaths have been reported[40, 62] (*6*) Even alcohol injections do not give permanent relief; in 14 of 75 patients there were recurrences within 2½ months.[62] (*7*) Intercostal neuralgia produces discomfort in all cases; *it is exceedingly* troublesome in 10 per cent, and may last for a long time.

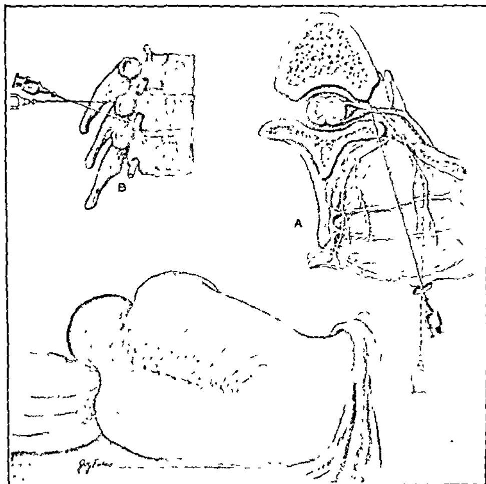


FIG 107 Thoracic paravertebral somatic nerve block dots indicate sites of injections A, Cross section B, Lateral view showing details of technic (From Bonica[12]

Various other methods of chemical nerve block have been suggested or tried Kux and Vetter[32] described a new approach for injection or fulguration, using endoscopy with direct vision Stubbs and Woolsey[54] have used bilateral stellate ganglion block with a buffered ammonium sulfate solution, with excellent results in 13 of 18 cases The injection must normally be repeated every 3 to 4 months and a bilateral Horner's syndrome must be achieved

Rinzler and Travell's[18] method consists of local block of referred neural impulses. Trigger areas are located, these are usually in myofascial structures, most often in relation to the pectoralis major and minor and the serratus anterior muscles. Procaine, 0.25 to 0 5 solution in physiologic saline, is injected, using a 23 or 24 gage needle 1¼ to 2 inches long. The total dose should not exceed 100 mg.

The procedure is usually effective only in *postinfarctive angina pectoris I have been* able to confirm the efficacy of the method in such cases Considerable relief is often obtained in atypical "cardiac pain," but typical angina pectoris is less frequently relieved. An alternative method is to spray ethyl chloride solution for 5 to 15 seconds over the trigger area; this gives shorter relief, but is useful for testing purposes

POSTERIOR RHIZOTOMY

In this procedure, the upper four or five thoracic roots are divided bilaterally White and Bland believe it to be the best operation in the best-risk group of patients, particularly if the pain is bilateral They report 3 deaths among 29 patients

The advantages of this method are (*1*) the technic is a standard one, well understood by the average neurosurgeon; (*2*) there is no possible chance of regeneration; and (*3*) the fibers can be cut on both sides at the same operation.

The disadvantages are: (*1*) time-consuming laminectomy of 4 vertebrae must be done; (*2*) risk of ischemic transverse myelitis as a result of bilateral root section, even if blood vessels are carefully preserved, (*3*) laminectomy, usually performed in the prone position, limits normal respiratory excursions and is poorly tolerated by many cardiac patients.

CERVICOTHORACIC GANGLIONECTOMY

In this operation, the stellate and upper thoracic sympathetic ganglions are removed on one or both sides. White and Smithwick[63] go down to the third thoracic segment (T3); Lindgren and Olivecrona[33] go down to the fourth or fifth segment (T4 or 5). The anterior approach is preferred. General anesthesia is used in most cases, although the sympathetic chain should be well infiltrated with procaine before it is manipulated.[33]

Lindgren reported on 105 cases treated in Sweden, a group of 88 patients not treated by operation serving as controls. The operative mortality was 8 5 per cent; the mortality rate up to 2 years postoperatively was the same in both groups. Bilateral rhizotomy was a two-stage procedure, the side with the worse pain being done first The second stage was deferred for at least 2 months. There was relief from pain in 75 per cent, about 66 per cent *reported increased capacity for work In about* a third of the cases, there was "migration of pain" to the neck or lower jaw (this may be seen after any type of neurosurgical procedure), and in 10 per cent this migration was serious enough to vitiate the result. In 1 such case, in which the patient was incapacitated by pain in the jaw, bilateral section of the descending root of the trigeminal nerve in the medulla resulted in complete recovery and relief from pain.

Even when angina pectoris was relieved, a "warning signal" remained. As with other neurosurgical procedures, a feeling of oppression, usually in the suprasternal notch, is a permanent residuum, and one which the intelligent patient will heed Anxiety is much alleviated The bilateral procedure slows the pulse but has no constant effect on blood pressure, heart volume, or the ECG Traumatic neuritis and nasal congestion may be troublesome. Contraindications are considered to be (*1*) infarction with previous hypertension and permanent drop in blood pressure, (*2*) electrocardiographic evidence of myocardial damage with cardiac enlargement; and (*3*) excessive or moderate cardiac insufficiency

Myocardial infarction has been reported after stellectomy, and a warning voiced against any operation "that suppresses the dilator system of the coronary circulation."[17]

PERICORONARY NEURECTOMY

In this procedure, as suggested by Fauteux,[21] especially in conjunction with ligation of the coronary vein, most of the nerve branches reaching or leaving the coronary arteries are destroyed. The procedure would seem to be useful in connection with other direct operations on the heart, but more hazardous than other neurosurgical procedures designed to interrupt nerve pathways. White

and Bland consider such an operation illogical from an anatomic point of view.

OTHER SURGICAL PROCEDURES

Angina pectoris may improve after other surgical procedures. Hufnagel[29] pointed out that in his operation for the correction of aortic insufficiency, 60 per cent of the patients with cardiac pain resulting from the valvular lesion improved Evans and Poppen[20] noted that angina pectoris was relieved in a large proportion of their patients who had a high thoracolumbar sympathectomy for the relief of hypertension Murray[44] has resected an infarcted area of the myocardium in 1 patient, who survived with good result; when the patient did die the heart was examined at autopsy, and appeared in good condition

Likoff and Bailey[37] have reported the successful excision of a ventricular aneurysm secondary to myocardial infarction. Cardiac function improved, and cardiac pain decreased DeCamp adds his own favorable experience.[17a] This operation will have to be watched attentively in the future. At the moment, there is little reason to believe that most such aneurysms add to the patient's disability or discomfort, nor do they change the prognosis except to indicate that there has been a severe infarction in the past.

CONCLUSIONS

The place of surgery in the treatment of coronary artery disease is far from settled However, so many advances are being made in surgical centers that basic physiologic problems are being clarified and general agreement on the nature of operative procedures and their indications seems likely soon

For the present, it appears that the small percentage of patients in whom angina pectoris is so intractable that medical therapy fails will benefit from some operations Of these, the use of talc in the pericardial sac (poudrage) seems so far the most successful. The addition of phenolization of the pericardium (de-epicardialization) may enhance the benefits of poudrage Neurosurgical procedures may be used in place of poudrage, or if the latter fails to give relief. In the last few years, we have been using fewer and fewer neurosurgical operations. On the basis of evidence thus far available, I am unable to recommend the other operations mentioned in this chapter. This attitude may be changed when further observations are reported or when experience dictates

Another avowed aim of the cardiac surgeons is to prolong life by preventing future infarction in persons with known cardiac disease This they may be accomplishing, but there is still no clear-cut evidence that they have improved the outlook for most patients. I would therefore prefer to wait for more definite evidence that the outlook for life has been increased before recommending surgery, except for those who have severe angina pectoris which does not respond to other forms of treatment.

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CHAPTER 19

Preventive Aspects of Coronary Disease

A[illegible] ease [illegible] able [illegible] our [illegible] ven [illegible] a d[illegible], we may hope one day to prevent it. There are not many things we can do at this moment, but there are a few and the paths for further investigation become constantly clearer. The main points of attack are. (*1*) adequate periodic survey; (*2*) prevention of atheroma, (*3*) prevention of infarction or reduction of the area of infarction, and (*4*) prevention of recurrence

The prevention of atheroma requires: (*1*) control of conditions associated with a high incidence of coronary sclerosis (obesity, diabetes, myxedema, hypertension, hyperlipemia, and polycythemia), and (*2*) measures designed to reduce blood lipids or their atherogenic properties, which include dietary restriction, and use of endocrine substances and other agents said to affect the blood lipids.

Prevention of infarction or reduction of the infarctive area calls for prompt treatment of early stages of infarction, for measures which will enhance the development of collaterals, for prompt treatment of shock, and for the prevention of thromboembolic complications

PREVENTION OF ATHEROMA

As we have seen, men past middle age are most susceptible, particularly those born into vulnerable families and those of a certain body build There is nothing we can do about our ancestors There is nothing we can do, little that we care to do, about changing our sexes, recently publicized cases notwithstanding. Most men are proud enough of what they consider to be the privileges and benefits of their masculinity to risk some curtailment of their lives from coronary disease; at least I have found none willing to give them up But there are other conditions, some which can be remedied, which increase the risk of this disease. All these have been considered in previous chapters but we may now discuss them briefly in their preventive aspects

Case finding here is at least as important as it is in tuberculosis The first step would surely be to include an electrocardiogram as part of the periodic health examination in persons over the age of 30 Those belonging to susceptible groups (family history, presence of frequently associated conditions) should have a special cardiac survey at least once a year, more often if there are suspicious symptoms This survey should include chest roentgenogram, ballistocardiogram, a stress test, and possibly an examination of the blood lipids Although these measures are not infallible, they will enable us to identify many potential victims before it is too late

OBESITY We need not a[illegible] our [illegible] and [illegible] treat [illegible] concede the desirability of maintaining a proper weight as a possible safeguard Most obesity is correctible but we must start with the child Family patterns of overeating, national food habits, parental oversolicitude must all be considered The physician will have to give due regard

to gluttony as an expression of emotional problems. Above all, he must convince patients and their families of the importance of maintaining proper weight. The educational programs of the insurance companies, the schools, and other agencies, may eventually have a beneficial effect on our eating habits. The American emphasis on nutrition translated into the quarts of milk, dozens of eggs, tons of butter, barrels of cod liver oil that we pour into our children, may perhaps be producing a nation overnourished but not physically fit. Recent responsible studies indicate that our well-fed children may be inferior in physical fitness to the sparer children of other cultures. In any case, leanness should be encouraged especially among members of the susceptible classes.[30]

Diabetes mellitus is associated with a high incidence of coronary atheroma. The use of high-fat diets in the treatment of diabetes, widespread in the thirties, may have contributed to this. We have good reason to believe that early and judicious control of carbohydrate metabolism, with resulting changes in fat metabolism, may lessen the number and severity of vascular complications.[32]

Myxedema requires vigilant control. Myxedematous persons are in urgent need of thyroid extract but tolerate only small doses. Overenthusiastic medication increases the work of the heart and may result in coronary insufficiency with anginal pain. Most patients require 3 grains or less a day.

Hypertension is often associated with coronary disease. Newer methods of therapy through medication offer some hope of effective control. At present, milder degrees of hypertension are usually left untreated, we hope that therapy will become safe enough for this group since coronary disease follows even lesser grades of high blood pressure.

Hypercholesterolemia, discussed in Chapter 3, whether familial or the result of disease, should be treated. Dietary fats should be reduced although only a measure of therapeutic success may be expected in most cases. Lipotropic agents may be tried but their benefits are questionable.

Polycythemia, which increases blood viscosity, is often associated with coronary thrombosis. It should therefore be treated.

MEASURES FOR REDUCING BLOOD LIPIDS OR THEIR ATHEROGENIC PROPERTIES

DIET See Chapters 4 and 20.

USE OF ENDOCRINE AGENTS The relative immunity to atheroma of young women has led to the use of estrogens in an attempt to prevent some of the ravages of this illness, even in men. The feminization which ensues after the prolonged use of female sex hormones would probably lead most men to forego the advantages of this method of treatment. Future developments along this line will command our closest attention.

OTHER AGENTS Many lipotropic agents have been proposed for the management of coronary disease. Some have been found useful in animals and are therefore being tried with enthusiasm in man with varying effect.

Lipotropic agents (choline, methionine, inositol) have been used extensively in animal experiments, and in a few cases in man.[5, 7, 9, 12, 13, 18-20, 22, 26, 27, 31, 33] The last word has not yet been said but there is no convincing evidence that atheroma can be retarded by giving patients lipotropic agents, singly or in combination. Caution should be exercised in using them in large amounts in persons with hepatic disease since they may be harmful to the liver.[10]

In a well-controlled study of 40 patients with angina pectoris, it was found that administration of a choline-inositol syrup gave no relief of symptoms. The mean levels of plasma cholesterol and phospholipid were not significantly affected during therapy. Fluctuations of these blood lipids were not significantly affected either.[15]

Various other therapeutic agents have been tried with as yet no very acceptable evidence that they prevent or retard the development of atheroma. Some of these are lipocaic; hyaluronidose,[25] Tween 80,[2, 16, 23] lecithin,[14] vitamins E and B_{12};[23] pancreatic extract.[28]

Iodides have been employed empirically in the treatment of arteriosclerosis for many years. Iodides in large doses have been reported to retard hypercholesterolemia and the development of experimental atheroma in rabbits, an effect independent of the thyroid gland.[8] Others feel that the iodides may have

some beneficial effect in man.[11, 13] On the other hand, some investigators find that potassium iodide fails to protect chickens from cholesterol induced atherosclerosis except in large doses[4] In smaller doses, it seemed to aggravate the lesions and elevate the blood cholesterol. Thyroid extract gave some protection in all doses. In rabbits, iodides intensity all the adverse effects of cholesterol feeding.[21] There seems little justification for the traditional use of potassium iodide

Heparin was noted, after the lipemia-clearing of heparin was observed, also to help convert cholesterol into lipoprotein particles of less atherogenic power. Unfortunately, we cannot utilize this action clinically since the use of heparin to obtain this effect would necessitate doses large enough to be hazardous The occasional injection of heparin by the employment of the depot technic has little effect on the circulating lipoproteins.[21] Sulfonated alginic acid, with a lipase-activating effect similar to that of heparin, is now under investigation by Constantinides at the University of British Columbia

Ultraviolet radiation has been reported to change cholesterol in some unknown way, making it less atherogenic in the rabbit[1] The same result is seen if the rabbit itself is irradiated, an effect not due to vitamin D. Serum cholesterol is reduced an average of 12 8 per cent in most persons 2 hours after a single ultraviolet irradiation, but in most there is a return to previous levels 24 hours later[1, 13] This is obviously a subject needing further investigation.

Plant sterols and unsaturated fatty acids are discussed in Chapter 4.

Nicotinic acid, in large doses up to 3 Gm a day, is now being used to lower the concentration of blood lipids in persons with hypercholesterolemia[1a, 22a]

Schroeder is investigating the attractive hypothesis that pyridoxal deficiency is important in atherogenesis[24a]

Other drugs such as phenylbutyramide and gallogen are currently under investigation for their defects in reducing the blood lipids

We think it quite likely that by reducing the lipids which are probably atherogenic, we may in fact be reducing coronary atheroma This is, however, still a working hypothesis which needs to be established in human beings.

PREVENTIVE ASPECTS OF ACUTE CORONARY DISEASE

PREVENTION OF INFARCTION OR REDUCTION OF INFARCTIVE AREA

When atheroma is already established, measures can still be taken to prevent infarction or to minimize its effects

Early infarction, even if small in degree, should be identified. The sudden advent of angina pectoris or abrupt change in the character, location, or mode of relief in established angina, should be regarded as evidence of infarction until proved otherwise. Such patients should be treated in the usual manner as described elsewhere in the text.

The premonitory signs of impending infarction should be recognized whenever possible. Severe precordial pain of a type not previously suffered by a patient who has known coronary disease or who is a candidate (member of susceptible group) should be regarded with suspicion Bed rest should be ordered, sedation and analgesics prescribed, serial cardiograms taken In many cases, it will be wise to order anticoagulant therapy to prevent possible thrombosis In those instances, a high percentage, in which infarction is not accompanied by arterial thrombosis, this procedure will be unnecessary but since one cannot be sure of the pathogenesis of the lesion in any given situation, it may be wise to use this treatment anyway

The survival of the patient or the size of the infarct depends largely on the availability of a collateral circulation Patients who have had sclerosis for some time will therefore have a better outlook than others, young victims are more likely to die suddenly Other factors, vigorous physical activity in the past, or previous anemia may have promoted the formation of a good reserve circulation "It is wrong to assume, however, that collateral channels, once established, remain indefinitely after the inciting factor has disappeared For example, despite the fact that anemia apparently promotes collateral circulation, it would probably be unwise to advocate the induction of anemia in man for prophylactic purposes.

At least 4 weeks of anemia are needed for collateral formation in dogs, and these vessels disappear when the blood returns to normal."[9]

In practice, however, the problem is to enhance the action of whatever collateral vessels the patient has. This means the alleviation of pain in order to prevent spasm of the *smaller arteries It means the prevention of* extreme hypotension in which the flow of blood from an intact artery is impaired because of reduced head pressure

Shock should therefore be treated early and vigorously along the lines suggested in the chapter on therapy The results of treatment are so far not encouraging but raising the blood pressure has the desirable effect of increasing the head pressure in the coronary arteries and preserving the collateral blood flow.

Anticoagulant drugs have obvious prophylactic value The chance of further thrombosis in the coronary vessels is reduced, the incidence of other thromboembolic events is lessened

Other complications of the acute infarction have preventive aspects It is probable that prompt bed rest early in the course of the illness helps to avoid aneurysmal dilatation Leg exercises help the anticoagulants to forestall the possibility of leg phlebothrombosis Physiotherapy to the upper arm and shoulder, especially active and passive motion, may reduce the incidence of the shoulder-hand syndrome

PREVENTIVE ASPECTS OF RECURRENCE OF INFARCTION

What can the physician and the patient who already has had evidence of definite coronary disease (angina pectoris, previous infarction) do about the prevention of recurrences? Some of the proposed measures are discussed elsewhere in this chapter The most important prophylactic steps, all of which are discussed extensively in other chapters, are. (*1*) Dietary measures aimed at correcting or preventing errors in lipid metabolism which might be associated with increased atherogenesis (2) Correction of obesity and other conditions thought to be connected with an increased incidence of atheroma. (*3*) Long-term administration of anticoagulant drugs. (*4*) Use of plant sterols. (*5*) Recognition and treatment of "impending infarction." (*6*) Avoidance of situations in which the blood pressure drops precipitately or for prolonged periods.

Patients with known atheroma (history of angina pectoris, previous infarction; electrocardiographic changes) should not, if possible, *expose themselves to situations in which* relative coronary insufficiency may result They should not engage in activities requiring sudden and sometimes unexpected physical or emotional strains Drugs which are potentially dangerous, such as pituitary extract or the newer hypotensive drugs, should be avoided or used with caution If smallpox vaccination, as mentioned in Chapter 2, is dangerous to coronary patients, it should not be done except when essential Blood pressures should not be lowered precipitously or for long periods anesthesia which may produce severe hypotension, *e g*, spinal anesthesia, should be avoided, in case of traumatic or hemorrhagic shock, every effort should be directed to raising the blood pressure The question of whether or not heart muscle will die depends on the ratio between the coronary blood flow and the demands of the muscle for nutrition When the coronary flow is sharply diminished, necrosis of the muscle bundles may take place in the absence of complete obstruction to blood flow Such conditions are completely realized in the case of a patient with a heart already enlarged by hypertension whose blood pressure falls rapidly in the course of an operation Such a heart is already, because of its increase in size, making excessive demands for nutrition and any failure of the coronary circulation because of reduced blood pressure may be fatal to the area supplied. Here is an excellent example of how *preventive medicine can be brought into operation* The blood pressure should not be permitted to fall to a marked degree during operation, especially in patients with enlargement of the heart or suspected involvement of the coronary vessels

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CHAPTER 20

Diet in Coronary Disease

THE THOUGHTFUL reader who has attempted to follow the literature regarding lipids and atheroma, some of which is summarized in Chapter 4, can scarcely be undismayed by the confusion and contradictions he has encountered Nevertheless, he will as a practicing physician attempt a fair evaluation of what he has read He will usually end by following one of three routes

First, he may take the exceedingly easy way of dismissing all the evidence and allowing the patient to eat whatever he pleases This course he will justify by pointing out the undeniable fact that there is as yet no completely conclusive evidence that dietary rearrangement or restriction of cholesterol and other lipids prevents or improves human coronary disease

Second, he may accept uncritically the views of some investigators and enthusiastically insist on extreme restrictions in the diet

Third, he may, as I do, steer to the middle of the road. He may find in the disorder, despite the inconsistencies of the literature, a direction which can hardly be disregarded He will then feel under an obligation not to wait *until every i is dotted and every t crossed* before giving his patient, if he can do so without harm, the benefits of a diet which seems to incorporate the best of current opinion, modifying it if necessary, as new reports are received.

In the last year, therefore, I have been prescribing a diet low in cholestrol and containing medium amounts of vegetable fats, with special emphasis on those derived from corn The caloric intake is reduced, if the patient is obese, until the weight reaches a satisfactory level All patients are advised to lose their taste for highly salted food, and to reduce the sodium content of the diet in view of the constant threat of decompensation. A restriction of salt consumption can usually do no harm.

BASIC DIET

An excellent basic diet is the low-cholesterol, low-fat diet compiled by Robinson * Normal levels of proteins are permitted Since the fat is greatly reduced, it becomes necessary to increase sharply the carbohydrate intake to maintain caloric balance unless, as often happens, weight reduction is also indicated. One of the chief obstacles to the use of this diet, however, is its reduced palatability, this can be overcome by the careful selection of foods and by the use of imagination in their preparation

Another invaluable source of information is the superb book, *The Low Fat, Low Cholesterol Diet.*** Every patient should be encouraged to get a copy. He will find innumerable menus, recipes and suggestions for varying the diet and making it more palatable In addition, diet lists for special conditions are given. For example, it is often necessary to modify this diet to restrict sodium as well. This is a much greater hardship than the basic diet and the patient will have much of the curse taken off by the suggestions given in the book Still another book which may be recommended is that of Field ***

As has already been said, the patient who

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* Robinson, C H *Am J Clin. Nutrition,* 2 353, 1954

** Dobbin, E V., Gofman, H F, Jones, H. C., Lyon, L, and Young, C B *The Low Fat, Low Cholesterol Diet* Garden City, N. Y., Doubleday, 1953.

*** Field, Florence *Gourmet Cooking for Cardiac Diets* Cleveland and New York, World, 1953.

has recovered from infarction should be encouraged to restrict his salt intake at least moderately. Many of these patients have, or have had, hypertension; none has an intact myocardium, and many will have decompensated hearts in the future Since Americans habitually use sodium chloride in amounts far in excess of basic needs, it appears wise to adjust one's appetite for salt as early in life as possible.

Patients with diabetes and coronary disease often need somewhat more insulin than do diabetics without complicating heart disease, since a relatively higher percentage of total calories is in the form of carbohydrates Obese patients usually have fewer difficulties. On the basic diet, with little added vegetable fat, most people lose weight.

BASIC DAILY DIET

(Nutritive value of listed foods *cholesterol*, 75 mg.; *protein*, 75 Gm ; *fat*, 25 Gm.; *carbohydrate*, 220 Gm.; *calcium*, 1,150 mg , *iron*, 12 mg ; *vitamin A*, 6,200 I U.; *thiamine*, 1 5 mg , *riboflavin*, 2.3 mg , *niacin*, 16 mg , *ascorbic acid*, 145 mg., calories, 1,400)

Skim milk (natural or prepared from dry milk)	3 cups
Lean beef, veal, lamb, poultry or fish	5 ounces
Whole-grain or enriched cereal	1 serving
Whole-grain or enriched bread	6 slices
Potato	1 (medium)
Leafy green or yellow vegetable	1-2 servings
Other vegetable	1 serving
Citrus fruit or other source of ascorbic acid	1 serving
Other fruits	2

(For additional calories use sugar, jelly, jam, or greater amounts of vegetables, fruits, cereals, or breads)

TO BE AVOIDED

Foods High in Cholesterol

Brains
Butter
Caviar
Cheese, all except skim-milk cottage
Cream
Egg yolk
Fish roe
Foods containing egg yolk, butter, whole milk, or cream; cake, cookies, eggnog, pastries, pie, milk and egg puddings, custard, egg noodles, griddle cakes, waffles, etc.
Heart
Animal oils and lard
Kidney
Liver
Mayonnaise
Milk, whole
Shellfish: oysters, clams, crabs, lobster, shrimp
Sweetbreads
Tripe
Fatty meat: bacon, ham, pork, mackerel, herring, fish canned in oil, duck, goose

Foods High in Vegetable Fat

(These may be added at the discretion of the physician)

Chocolate
Nuts
Vegetable fats and oils, including salad dressings:
Crisco
Kraft oil
Mazola
Olive oil
Peanut butter
Peanut oil
Soybean oil
Spry
Wesson oil

MENU PATTERNS

The following menu pattern is one way in which the foods in the above list might be arranged

Pattern Menu	Sample Menu
Breakfast	
Fruit, preferably citrus	Half grapefruit
Cereal	Oatmeal with sugar
Skim milk—1 cup	Skim milk—1 cup
Bread—2 slices	Whole-wheat toast—2 slices
Jelly, jam, or marmalade	Orange marmalade
Hot beverage	Coffee, with sugar, if desired

Luncheon or Supper

Clear soup, if desired	Consomme
Lean meat or cottage cheese	Sandwich of 2 ounces lean roast beef, 2 slices rye bread, lettuce, prepared mustard
Bread—2 slices	Celery and carrot sticks
Green or yellow vegetable	Skim milk—1 cup
Skim milk	Fresh fruit cup
Fruit	

Dinner

Lean meat, poultry, or fish	Baked flounder with Creole sauce
Potato or substitute	Steamed rice
Green or yellow vegetable	Zucchini squash
Bread—2 slices	Bread—2 slices
Jelly or jam	Grape jelly
Fruit	Angel cake with fresh strawberries
Skim milk—1 cup	Skim milk

SPECIAL FOODS

Usually the individual becomes accustomed to skim milk and in time may even prefer it to whole milk Such a simple expedient as serving the milk ice cold deserves emphasis because so often this precaution is not taken Skim milk may be used successfully in the preparation of cornstarch puddings (without egg), in cream soups thickened with a little flour-water paste (no fat), in cocoa-flavored beverages, and in the preparation of fruit ices

Cooked vegetables may be seasoned with pepper or a variety of herbs and spices A dash of nutmeg on green beans, peas cooked with mint, corn with tomatoes, just a speck of mace with potatoes mashed with double-strength skim milk (made from nonfat milk solids) suggest a few possibilities for adding flavor appeal when fats are missing Occasionally, vegetables may be cooked in a small amount of fat-free broth for taste variety.

An addition to the basic list which will add flexibility is the sodium-poor, fat-poor cottage cheese now obtainable in some cities The cheese may be seasoned with caraway seeds, celery seeds, black pepper, chopped fruit, jams or jellies, chives, sugar, or cinnamon

In large cities, "low fat" cheeses are sometimes sold in large or special markets The patient should use extreme caution in purchasing these because they may vary in butter fat content from 7 to 14 per cent; regular milk cheese has about 30 per cent butter fat content Nevertheless, carefully used, these may add welcome variety to the diet on days when meat or fish is not used.

Acceptable salad dressings are also prepared and sold under commercial labels. Among these are an attractive mayonnaise-type dressing, a French dressing, and a dressing made with herbs

Noodles made with egg yolks cannot be used, but green noodles (Buitoni) are a useful substitute, since they are made without fat or added salt Some white cake mixes now on the market are made without egg yolks and therefore are acceptable as part of a low-cholesterol diet

MENUS FOR ENTERTAINING

One of the hardest things for patients to do is to regulate their diets when they are in company If eating were as private as bathing, there would be no problem, but since food is the inevitable accompaniment of social life, patients may be tempted either to abandon their diets or to give up seeing their friends—with equally disastrous results I am including several menus, made up mainly of low-cholesterol foods, which are suitable for dinner parties No attempt has been made to give the exact amounts of cholesterol per portion and no attempt has been made to restrict sodium The salient feature of these menus is their resemblance to ordinary dinner menus, it is doubtful whether any guest would notice anything out of the way or "dietary" about any one of them Butter for the bread and cream for the coffee may, of course, be added by the guests Recipes for most of the dishes may be found in standard cookbooks, such as *The Settlement Cook Book* or the *Joy of Cooking* Amounts given will serve 6 "dieters" or 1 "dieter" and 3 or 4 guests

MENUS

I

Hot tomato juice	String beans
Veal with cherries	Cocoa sponge or apricot whip
Brown or white rice	

II

Raw vegetable plate: cauliflower, carrot sticks, celery, radishes, tomatoes

Chicken curry with rice, garnished with chutney, chopped hard-cooked eggwhite, shredded coconut, raisins

Baked peaches, pears, or apples

Caramel meringue kisses

III

Fresh fruit cup Any combination of oranges, pineapple, grapefruit, bananas, berries, and melon in season, a little Cointreau or Sherry may be added

Beef stew with vegetables

White cake with hot maple syrup

IV

Broiled or plain grapefruit

Roast leg of lamb

Mashed potatoes (use skim milk with salt, omit butter)

Peas with mushrooms

Brandied chocolate dessert

V

Vegetable soup

Baked halibut with tomato or mustard sauce

Oven fried potatoes: use oil to coat cubed potatoes and bake in the oven with halibut.

Asparagus vinaigrette

Cocoa angel cake (add cocoa to Swansdown or Betty Crocker angel cake mix)

VI

Italian spaghetti with meatless tomato sauce and grated Parmesan cheese (the cheese will substitute for the meat in this meal)

Tossed green salad

Italian bread (The popular "garlic bread" may be made by brushing a small amount of olive oil flavored with garlic on the thickly sliced bread and toasting in the oven)

Fruit sherbet or fresh fruit

VII

Jellied bouillon

Green peppers filled with meat and rice

Baked tomatoes

Baked potatoes

Carrot sticks and radishes

Meringue shells filled with frozen fruit

TABLE 27. APPROXIMATE CHOLESTEROL CONTENT OF FOODS
(From *The Low Fat, Low Cholesterol Diet*)

Food	Cholesterol in 100 Gm portion, mg.	Approximate cholesterol content of unit	
		household measure	*mg.*
Meat and meat products			
Bacon, crisply fried	100	2 strips	16
Beef, lean	100	¼ lb.	110
medium fat	125	¼ lb	140
Bouillon cube	None	None	
Chicken	75	¼ lb.	85
Duck	70	¼ lb.	80
Fish			
Codfish	50	¼ lb	60
Codfish-liver oil	500	1 tb	75
Halibut	60	¼ lb	70
Halibut-liver oil	7,500	1 tb	1,000
Salmon	60	¼ lb	70
Sole, cooked	60	¼ lb	70
Tuna, canned (oil removed)	60	¼ lb	70
Frog legs	40	¼ lb	50
Lamb, muscle	70	¼ lb.	80
Lard	110	¼ lb	125
Marrow fat	300	¼ lb	350
Organ meats			
Beef Brains	2,000	¼ lb	2,300
Heart	150	¼ lb	170
Kidney	400	¼ lb	450
Liver	250	¼ lb	280
Lungs	400	¼ lb	450
Calf liver	400	¼ lb	450
Lamb liver	600	¼ lb.	700
Pork liver	400	¼ lb	450
Sweetbreads	300	¼ lb	350
Tripe	150	¼ lb.	170
Pork, lean	60	¼ lb	70
Rabbit	75	¼ lb	85
Soup stock, fat removed	None	None	
Turkey	75	¼ lb	85
Turtle	60	¼ lb	70
Veal Shank	100	¼ lb.	110
Breast	100	¼ lb	110
Muscle meat	65	¼ lb.	75
Dairy products			
Butter	300	¼ lb	350
Cheese			
American	150	¼ lb.	170
American process	150	¼ lb.	170
Cottage cheese, dry curd	1.7	¼ lb	2
"Special"	1.4	¼ lb.	1.5
Edam (imported)	60	¼ lb	70

TABLE 27. APPROXIMATE CHOLESTEROL CONTENT OF FOODS (*Contd*)
(From *The Low Fat, Low Cholesterol Diet.*)

Food	Cholesterol in 100 Gm. portion, mg.	Approximate cholesterol content of unit	
		household measure	*mg*
Dairy products (contd.)			
Limburger process	150	¼ lb	170
Monterery Jack	150	¼ lb.	170
Parmesan	60	¼ lb	70
Pimento cream process	150	¼ lb	170
Roquefort	100	¼ lb.	110
Swiss process	150	¼ lb	170
Velveeta	150	¼ lb.	170
Cream, Table (25% fat)	87	½ pint	220
Whipping (40% fat)	140	½ pint	350
Eggs (hen's)			
Yolk	1,400	1 yolk	300
White	None	None	
Milk: Nonfat (1% fat)	0.4	½ pint	1.0
Skim milk powder (1% fat)*	3.5	½ cup	2.1
Whole (4% fat)	14.0	½ pint	35
Fruits and vegetables			
All fruits and fruit products	None	None	
All vegetables and vegetable products	None	None	
Miscellaneous			
Alcoholic beverages	None	None	
Cocoa and chocolate	None	None	
Coffee	None	None	
Gelatin	None	None	
Grains and grain products	None	None	
Herbs	None	None	
Honey	None	None	
Jams	None	None	
Jellies	None	None	
Legumes	None	None	
Macaroni	None	None	
Marshmallows	None	None	
Molasses	None	None	
Nuts	None	None	
Salt	None	None	
Spaghetti	None	None	
Spices	None	None	
Sugar	None	None	
Syrup (maple and corn)	None	None	
Tapioca	None	None	
Tea	None	None	
Vanilla and other flavoring extracts	None	None	

* Some skim milk powders, in which the fat is less completely removed, have been found to be slightly higher in cholesterol

CHAPTER 21

Medicolegal Aspects of Coronary Disease

THE CARDIOLOGIST, regarding himself primarily as a scientist and endeavoring to preserve for himself the same serenity as he prescribes for his patient, has recently found himself unwillingly and increasingly involved in burdensome litigation, arising in good part from Workmen's Compensation and insurance claims.

TRAUMA AND THE CORONARY ARTERIES

The heart may be damaged in direct trauma to the chest[18] While the bony framework of the chest protects the viscera within it in most cases, cardiac damage may occur when the chest is struck by a hard object, when it is injured in a fall, or in automobile accidents involving impact with a steering wheel The frequency of such traumatic lesions is under considerable dispute. Some consider them extremely rare, others quite common Factors which may influence the effect of such trauma on the heart are

1. The resilience of the thoracic cage, which is decreased with advancing age, an injury is more likely to damage the heart in the young, who have elastic chest walls.[1]

2. The presence of heart disease,[19] sclerotic vessels are more easily injured and intramural hemorrhages may result

3. A tendency to psychoneurosis or vagosympathetic imbalance,[16] or administration of digitalis, thyroxine, or epinephrine before the injury may constitute a sensitizing factor

Various injuries have been described. The heart tissue may suffer direct injury or injury secondary to circulatory changes due to trauma, in the latter case, the lesion is similar to that occurring in infarction after coronary occlusion[13] After chest trauma, the heart may be violently thrown against the bony parts and compressed[10] It may be torn from its attachments, have its walls lacerated or ruptured, have the blood forced back into the ventricles or prevented from leaving by compression, or be bruised by fractured bones pressing against its surface The pericardium may be injured In rare cases, the valves may be ruptured. The coronary vessels may be injured and intimal hemorrhage, as described by Patterson,[13a] may result Actual thrombosis of a coronary artery after this type of injury is exceedingly rare.

In experimental animals, death may occur without extensive lesions and in survival experiments extensive lesions may produce little evident dysfunction In studies with cats and rabbits that died after receiving mallet blows to the chest, 90 per cent showed no structural damage to the heart[15] Changes other than tissue trauma may account for death in some instances. Such changes would be reflex *coronary spasm, cardiac dilatation, and spasm* caused by direct, rather than reflex, action of the vibratory forces on the coronary vessels Death is more likely to follow trauma in animals sensitized with heterogenous serum,[15] or those under the influence of digitalis, thyroxine, or epinephrine[7]

Considering the many possible anatomic variations of cardiac injury in such cases, the absence of a clear-cut clinical picture is not surprising The clinical descriptions in the literature for the most part lack either postmortem data or adequate clinical study. In

one group of cases, the most common symptoms were pain, dyspnea, tachycardia, dizziness, unconsciousness, and weakness.[10] In another group, a dazed feeling, dizziness, or unconsciousness were the first manifestations of injury.[16] After a latent period, precordial pain, weakness, or even angina pectoris which may persist for months or years, may appear. Dyspnea and palpitation are other complaints. Objectively, the most common findings were poor heart sounds, rate and rhythm disturbances (although not nearly as often as in experimental animals), systolic murmur, normal blood pressure, and changes in the electrocardiographic pattern. The latter may resemble the progressive findings in the myocardial infarction of coronary disease. Other cases may show arrhythmias, QRS complex changes, and nonspecific alteration of the S-T segment or T wave.

Coronary occlusion resulting from direct trauma to the chest is rare In exceptional cases, when the artery lies in, or close to, the area of injury, the vessel wall may be injured and thrombosis may ensue The following case reports are examples.

Case 1. A 58 year old man with syphilis, hypertension, and known coronary disease for many years, had his manubrium sterni fractured in an automobile accident, 8 hours later he had precordial pain and died, autopsy showed recent thrombus in a sclerosed coronary artery.[17]

Case 2 A 50 year old woman with previous hypertension complained of chest pain immediately after being thrown against the seat of a car in an automobile accident The electrocardiogram showed evidence of coronary thrombosis with myocardial infarction She died suddenly on the thirteenth day and the autopsy corroborated the recent occurrence of the lesion

Coronary thrombosis after blunt injury to the chest was reported in 7 cases[19] Coronary occlusion has been noted as one of the sequelae of such injuries,[2] and 2 cases resembling posterior wall infarction after blunt injury to the chest in young men have been reported[5] Other apparently authentic cases have also been reported[6, 9]

From a medical point of view, there is little difference in the electrocardiographic or clinical features of a heart wall injured by direct contusion, whether or not the coronary artery is occluded In either case, infarction, fibrosis, or rupture of the myocardium may result. However, the outlook would be distinctly more favorable in those cases in which the myocardium alone is involved.

Most injured hearts heal without evident functional disability. Healing is by fibrosis and seems to be very similar to that which occurs in the heart wall after coronary thrombosis. In some instances, partial or total disability is claimed as a result of the accident. In such cases it may be extremely difficult to evaluate the relation between the trauma that had been suffered and the symptoms and signs which are found The history is of the utmost importance, and every effort should be made to obtain as reliable a story as possible The history should cover the previous health of the patient, the nature of the symptoms and the time of their appearance following the accident, and the nature of the injuries sustained An ECG should be taken soon after the accident, and frequently thereafter.

WORKMEN'S COMPENSATION CLAIMS*

No aspect of coronary disease is so troubling and exasperating to the cardiologist as the relation of the disease to injury and exertion He will be faced by this mostly in Workmen's Compensation cases, and when called on to testify will sometimes wish that he had chosen another profession. The physician may be unable to answer with assurance the questions put to him, even when he is thoroughly familiar with this illness, has spent years in study of its course and vagaries, has the literature of other investigators at his command, and when he exercises honesty, good will and cautious judgment.

Contrary to common belief, workmen's compensation laws are not a development of the English common law or of employer's liability legislation but an outgrowth of the increasing number of accidents after the Industrial Revolution and new philosophic concepts In 1881, Bismarck, worried about

* I have drawn considerably on several sources for this section· Clark, Tousant, and Sprague;[4] Texon,[14] and Larson[8] The last mentioned has written a most comprehensive and authoritative treatise on the subject.

Marxian strength in earlier elections, had the *first compulsory insurance laws passed in an* effort to block what he feared to be an advancing tide of socialism. In 1884, the first compensation law was passed in Germany—13 years before England, 25 years before the first American legislation, and 65 years before the last American state (Mississippi) followed suit In 9 of the United States, workmen's compensation is not industrywide but limited *to specially hazardous occupations*

American legislation started in 1909. New York passed its first law in 1910 The next year it was held to violate the state constitution, in 1913, this was remedied by a New York State constitutional amendment which was finally, in 1917, upheld as constitutional by the United States Supreme Court Thereafter, the way was open for all the states to *pass suitable laws As early as 1912*, a Workmen's Compensation Act was passed in Massachusetts to cover personal injury As defined by decisions of the state Supreme Judicial Court, it now includes disease and accidental injury to the body or mind, direct or indirect, arising out of, or in the course of, employment Also, "aggravation of a pre-existing disease to the point of disability or to a fatal ending sooner than would have occurred shall be a personal injury provided it is caused by the strain or exertion of work, but not if it is due to the natural effect of exertion on an organ already diseased" Uniquely *American is the fact that the employer alone* makes contributions, neither the state nor employee bearing a share. The theory is that this is a legitimate part of the cost of manufacture and is therefore passed on to the consumer in the price of the finished product.

It is fundamental to an understanding of the compensation system to know that its underlying philosophy is that of social pro*tection rather than of righting a wrong* The basic test of liability is connection with work rather than the "fault" of anyone. The right to benefits is based largely on the assumption of providing support or preventing destitution rather than of settling accounts between two individuals according to their deserts or blame. The test is whether a situation "arises out of employment" not whether it is "proximately caused by employment", the question whether an employee's fault is a contributing factor, for example, is therefore largely disregarded.

How have the original American laws been modified and reinterpreted to bring about the present attitude of compensation tribunals toward cases involving the heart? These changes have revolved around the interpretation of some key words and phrases. Of these, the first to undergo transformation was the phrase "by accident," a phrase found in most statutes and meaning an "unlooked for mishap *or untoward event which is not expected* or designed." The basic factor in the concept of "accident" is unexpectedness. But what is it that has to be unexpected, the cause of the result? If courts insist that the cause of an injury be an "untoward" or "unexpected" event, then the number of cases involving the heart will be comparatively small, when the result of a given performance, regardless of *its nature, is unexpected and is then regarded* as accidental, the number of compensable cases will be much larger. This distinction will become clearer when the "usual vs. unusual event" concept is considered.

Another aspect of the word "accident" which is important is whether "by accident" or "accidental" one means "by an accident" If it is so construed, and some courts have done and are doing so, the claimant must be able to fix the date with some degree of certainty. However, many courts, including those of New York State, have held that the cause may be gradual and imperceptible and *still be accidental. This of course leads to a* considerable expansion of the number of compensable heart claims

In the past, and in some states even now, an exertion, to be considered accidental within the meaning of compensation laws, had to be "unusual" and not in the line of the patient's ordinary duties. This has been a difficult attitude to maintain, and many ambiguities and hairline decisions were involved. In the last few years, the interpretation, if not the letter, of the law has become somewhat standardized and clarified.

Two types of incidents are commonly distinguished. In the first, in which "usual exertion leads to something actually breaking, herniating, or letting go, with an obvious sudden mechanical or structural change in the body," the injury is considered accidental by most jurisdictions; an overwhelming majority

will therefore compensate for ruptured aneurysm, even when the exertion or conditions producing the change are in line with the usual duties of a job. The second type of incident, which involves subtler arguments, is "injuries from generalized conditions" A much narrower majority of jurisdictions accept usual exertion as leading to accidental injury when it involves coronary thrombosis and other cardiac conditions. The following are representative cases:

Compensation was allowed and the usual-exertion rule definitely stated in the case of a man who had a coronary occlusion in the course of his usual work of stacking 135 pound grain sacks (Warlich v. Driscoll, 68 Idaho 522, 200 P.2d 1014 (1948).

Compensation was allowed for a coronary thrombosis from lifting sacks of sugar in the usual way (Peterson v Safeway Stores, 158 Kan 271, 146 P 2d 657 (1944).

Compensation was allowed in the case of a deputy sheriff who suffered a coronary occlusion while smashing stills in his usual way (Willis v Aiken County, 203 S C. 96, 26 S E.2d 313 (1943).

Death from coronary occlusion was held to be accidental and compensable in the case of a man who worked extremely long hours during the height of pea-picking season for 3 days (Jones v. California Packing Corp. Utah 244, P2d 640 (1952).

Larson[8] cites Georgia as a good example of a state which has carried to its ultimate expression the reasoning that an unexpected result is sufficient to supply the accidental element, whether the cause is extraordinary or not. It follows the formula that "An accident arises out of the employment when the required exertion producing the accident is too great for the man undertaking the work, whatever the degree of exertion or the condition of health"

Applying this rule, Georgia has actually found heart failure to be an accident when the exertion, far from being unusually heavy, was lighter than usual—so long as the exertion in fact precipitated the attack (Lumbermen's Mutual Casualty Company v Kitchens, 81 Ga. App. 470, 59 S E.2d 270 (1950). In this case, decedent had asked to be put on lighter work because he was not feeling well, and at the time of his death he was carrying 1×4 boards, none of which weighed over 20 pounds—about the weight of a portable typewriter or a pail of water. Yet, because of his extremely bad heart condition, even this exertion could, as was established by the medical testimony, bring on the collapse In the same month, Georgia awarded compensation for a heart attack suffered 5 minutes after a bookkeeper had walked up a single flight of stairs to his office (Bussey v Globe Indemnity Co, 81 Ga App. 401, 59 S E 2d 34 (1950).

The attitudes of New York and New Jersey deserve special attention, since they are the states which have produced the largest volume of disputed heart cases New Jersey has adopted the usual-exertion theory, as have most states, for most kinds of injury, while insisting on "unusual exertion" in cardiac cases Nevertheless, the New Jersey reports are filled with finely balanced distinctions on which exertions are usual and which unusual in heart cases

New York State, with the largest number of cases, started by insisting emphatically on unusual or even catastrophic circumstances Judge Pound, speaking for a unanimous Court of Appeals, laid down the rules

A distinction exists between accidental injury and disease, but disease may be an accidental injury The exception arises out of abnormal conditions which must be established to sustain an award Two concurrent limitations have been placed on the right to recover an award when a disease, not the natural and unavoidable result of the employment, is developed during the course of the employment, although it does not follow that compensation should be awarded in all cases coming literally within these limitations First, the inception of the disease must be assignable to a determinate or single act, identified in space or time (Matter of Jeffreyes v Sager Co, 198 App Div 446, 233 N Y 535) Secondly, it must also be assignable to something catastrophic or extraordinary (Matter of Connelly v Hunt Furniture Co, 240 N Y 83)

Almost immediately, courts found it difficult to decide the nature of an unusual exertion Finally, in 1943, compensation was allowed in the case of a furnace stoker who collapsed after throwing a dozen shovels of coal, each weighing about 40 pounds, on the fire. This was held an accidental injury, in spite of the fact that the shoveling was his regular job (Bohm v L R.S & B. Realty Co., Inc, 264 App Div 962, 37 N Y.S. 2d (1942)

aff'd 289 N Y. 808, 47 N.E. 2d 52 (1943) In 1944, a plant patrolman's coronary occlusion was ruled to be accidental because he had to patrol an outside beat in extreme cold during a heavy snowstorm, although of course his regular job was to patrol in all kinds of weather (Flammer v Bethlehem Steel Co, 268 App Div 944, 51 N Y S 2d 258 (1944), aff'd 295 N Y. 817, 66 N E 2d 588 (1946). The same year, the exertion of a fireman who ran up two flights of stairs, halfway down, and then up again was held "unusual," although realistically it was surely a routine activity for a fireman (Godsman v. Grumman Aircraft Engineering Corp, 268 App Div. 945, 51 N Y S 2d 760 (1944), aff'd 295 N.Y 708, 65 N E. 2d 339 (1946) And in 1945, the necessity of remaining in a cramped position for an hour to tamp new firebrick inside a boiler was held to convert the strain into an accidental injury (Brooks v. Elliot Bates, Inc., 269 App Div. 792, 55 N Y S 2d 671 (1945), aff'd 295 N Y. 710, 65 N E 2d 340 (1946), two Judges dissenting)

With the Cooper case in 1946, the newer view begins to affect even the language of the opinions, reference to the unusualness of the exertion being sometimes omitted altogether In this case, an award was made for the death of a trucker who had put in an unusually hard day, lifting 2 cartons at a time in order to save time, because he had no helper. The Appellate Division's opinion said that "the board could find that the heart attack which caused the death was produced by the labor incident to the employment" (Cooper v. Brunswick Cigar Co, Inc., 273 App Div 1038, 78 N Y S 2d 642 (1949), aff'd 298 N.Y 731, 83 N E 2d 142 (1948))

From 1948 on, a series of cases emerged which reduced the distinction between usual and unusual to a hollow shell In one case, a painter had so placed his ladder that he had to stretch his arm "all the way out" in order to paint, and the Appellate Division held that the "extreme exertion and extension of his arms in painting" satisfied the requirement of accidental injury (Ruby v Lustig, 274 App. Div. 954, 83 N Y S 2d 664 (1948), aff'd 299 N.Y. 759, 87 N.E. 2d 672 (1949) In another, a deliveryman who suffered a heart attack while carrying a 60 pound case of beer was granted compensation, the only nonroutine feature being the fact that the driveway on which he was walking was somewhat slippery (Serie v. F. & M Schaefer Brewing Co., 273 App. Div 833, 76 N.Y.S. 2d 50 (1948). But, to show that the old requirement could still defeat claims, in the same year the same court denied compensation for the death of a house superintendent who suffered a coronary occlusion while carrying downstairs garbage cans weighing 70 pounds—10 pounds more than the beer cases and on the stairs at that (Chiara v Villa Charlotte Bronte, Inc., 273 App Div. 834, 76 N.Y.S. 2d 59 (1948), aff'd 298 N.Y. 604, 81 N E. 2d 332 (1948).

Then came a series of cases in which it was ruled that to show catastrophe the only proof needed was that the decedent had been working harder than he had used to work at some time in the past. In the Furtado case, the claimant, upon being promoted to the responsible job of supervising construction of 3 new shops, worked long hours 7 days a week for 9 or 10 months, and experienced heart symptoms from time to time; the Appellate Division found this assignment to be "unusual work," and held that "claimant sustained accidental injuries arising out of and in the course of employment due to long and arduous hours of work." (Furtado v American Export Airlines, Inc, 274 App. Div 954, 83 N Y.S 2d 664 (1948), leave to appeal denied, 298 N.Y. 933 (1949). In 1949, an inspector was brought within the protective orbit of "accident" solely because "the work done by claimant had about a month earlier been changed so that fewer men were doing the same volume of inspections which increased claimant's physical effort" (Carlin v Colgate Aircraft Corp., 276 App. Div 881, 93 N.Y.S 2d 791 (1949), aff'd 301 N.Y. 754, 95 N E. 2d 626 (1950). In other words, a strain which has been usual and routine for a month is an "accident" because a month earlier the claimant had had lighter work.

At about this time, the Court of Appeals apparently felt that it had had about enough of this sort of thing, and in Masse v. James H Robinson Company (301 N.Y. 34, 92 N. E 2d 56 (1950), reversing the lower court, it awarded compensation to a man who had undergone unusually arduous work during the

week preceding a heart attack which occurred at home, and made the following unqualified statement:

"A heart injury such as coronary occlusion or thrombosis when brought on by overexertion or strain in the course of daily work is compensable, though a pre-existing pathology may have been a contributing factor."

Nothing was said about unusual strain, the quotation permits recovery not only for overexertion but for "strain in the course of daily work."

Since the Masse case, awards have been sustained on the basis of the following exertions: "pulling" a machine which claimant regularly pulled seven times a day, climbing the subway stairs, with no evidence whatever of special haste; long hours and unusual excitement causing the death of the steward of a social club; erecting partitions in a store, which claimant regularly did "at certain seasons," on the assumption, apparently, that what is done most of the time is usual, and what is done only some of the time is unusual and accidental, spending 1½ hours in and out of a refrigerator while repairing it, which was "the longest period of time which claimant had been required to spend in a refrigerated box", working harder than usual as a bookstore clerk in some unspecified degree for some unspecified time, thereby making a detached retina in the eye an accidental injury; and spending 5 or 10 minutes in the usual cramped position a steamfitter has to assume while working inside a boiler. In this last case, the court made a statement which sums up the story from the Lerner to the Masse case

> Appellants cite the definition of an accident as something extraordinary or catastrophic, assignable to a determinate or single act, identified in space or time
>
> As an abstract legal proposition undoubtedly this definition is unassailable. However whether an event is to be found an industrial accident is not to be determined by legal definition "but by the common-sense viewpoint of the average man" [Citing the Masse case] Hence the issue almost invariably falls within the realm of fact, and if the facts and circumstances sustain, upon any reasonable hypotheses the conclusion that an average man would view the event as accidental, then the determinative facts and circumstances were presented in the instant case, and that common men would regard decedent's injuries as accidental. At least we cannot say as a matter of law that such is not the case Applications of this principle, though often not expressed, are inherent in many decisions

What if the worker was aware of having cardiac symptoms and continued working? New York and New Jersey hold that continuing a usual exertion after becoming aware of illness makes the episode accidental Contrariwise, Pennsylvania holds that if the claimant was in good health and suffered a heart attack in the course of routine exertion, he had had an "accident" If, however, he had previous disease, unusual strain must be shown to prove an accident

Most of these mental acrobatics which baffle the nonlegal mind arise from the use of the word "accident" in one form or another in the older laws The purpose of this usage and of the distinction drawn between "usual" and "unusual" exertion is to prevent claims being made for disease processes which have no relevance to a man's work. However, there is another method of establishing this safeguard in a more realistic manner, without the clumsy device of the "accident," a device which invites relaxation, modification, and some kind of evasion in order that justice may be done In some states, the concept of "accident" is avoided altogether and it is required that the injury arise "out of employment" As Larson shows, an examination of cases in such states, for example, California, Iowa, and Massachusetts, getting an "exertion of exposure" award is not necessarily easy; the only difference is that the issue is joined at the proper point, whether or not there is fundamental causation rather than an accident. There must still be an unexpected result and some exertion which could cause the collapse The mere fact that a breakdown occurs during working hours is not sufficient, there must be some effort which establishes a causal connection Here, medical testimony becomes of even greater importance than ever before

The physician may, at least in New York, concede that practically all infarction has its origin in underlying atheroma without compromising his patient's claims The real issue is the relation of a given exertion or stress incident to an episode of infarction

How can we simplify a problem which

defies simplification? We can start with the assumption that coronary occlusion almost never occurs in an intact coronary artery. Underneath the occluded section of the vessel there is almost invariably an area of atheroma; this is an abnormality, but whether, before ischemia results, it can be considered disease, is controversial Certainly atheroma, even of high degree, is compatible with long and useful life. Other causes of coronary occlusion, such as embolism, are rare, and to my knowledge none of them have been brought into question with regard to the compensable aspects of coronary disease.

The pertinent pathologic changes need only brief summary here The transition from atheroma to occlusion may take place in several ways: (*1*) rupture of the atheroma with discharge of its contents, (*2*) hemorrhage into the plaque, which then expands and may rupture; (*3*) thrombosis on a plaque which has either an intact intima or a lining disrupted by hemorrhage or rupture. Just how injury or strain would affect this transition is doubtful, but presumably sudden increase in blood pressure would be a factor This is at least moderately plausible in the case of intimal hemorrhage, although there is still doubt that changes in blood pressure are transmitted to the intimal capillaries.

Infarction may of course occur in the presence of coronary sclerosis without occlusion of a major vessel. A schematic portrayal of this process is given in Chapter 1. There may be thrombosis or spasm of a smaller vessel, possibly a collateral channel An important factor in producing infarction in cases of injury is the hypotension of shock or hemorrhage; I have seen several examples In an otherwise impaired heart, the drop in blood pressure may be sufficient to induce infarction through ischemia. This could happen in a heart with normal arteries, but the hypotension would have to be profound and prolonged.

It is impossible to give unimpeachable criteria for determining whether an infarction or coronary occlusive episode is the result of a given injury or stress. I am fairly certain that many more cases have been acknowledged in litigation than are warranted in fact, perhaps on the assumption that the law should be liberally construed in favor of the claimant or his family. Nevertheless, I have seen instances in which every criterion of common sense would indicate the existence of such a relationship.

Case 3. A 56 year old man tripped and fell down a flight of 18 steps while struggling to maintain his hold on a keg of nails in his arms. Within a few minutes of the time he was picked up, he complained of pain in the left side of his chest, which at first was attributed to rib fracture. An hour later, profuse perspiration appeared, and his systolic blood pressure dropped from 150 to 100. An ECG was read as normal, but 6 hours after the fall changes were evident and the course was then that of an anterior infarction.

With such a story, if called upon, I would testify in clear conscience that the infarction was the result of the circumstances of the fall Whether or not there was a direct blow to the chest during the fall seems to me immaterial.

Usually the story is not so clear cut, and in such cases the criteria set forth by Blumgart[3] are a useful guide to clinical judgment. He listed the following criteria which must be satisfied to demonstrate the relationship of effort to myocardial infarction: (*1*) development and increase of cardiac symptoms, such as pain or substernal distress, during or immediately following unusual effort, (*2*) continuation of the symptoms after cessation of effort, (*3*) presence of clinical signs and symptoms of acute myocardial infarction, (*4*) development of characteristic electrocardiographic patterns of infarction

While this list is a useful guide, it should nevertheless not be interpreted rigidly. Each one of the criteria may be modified under certain circumstances.

It is unwise to insist that symptoms be absolutely continuous after onset. As in naturally occurring infarction, there may be a period of remission corresponding to partial interruption of coronary flow and partial ischemia of the heart muscle.

Case 4 A 42 year old man, with angina pectoris, ran upstairs with a television set weighing about twice the usual amount. When he arrived at the head of the flight of stairs, he collapsed with severe precordial pain radiating to the left arm The pain did not respond to the nitroglycerin which he had with him, but subsided after a few moments. He had more angina of effort that afternoon, but was free of pain

while lying in bed for 6 hours, a typical infarction developed that evening

In this case, there can be little doubt of a relationship between the injury and the cardiac catastrophe, and I had no hesitation in giving my opinion to that effect.

With regard to the third and fourth criteria, the alert clinician will bear in mind the frequency of atypical signs, symptoms, and laboratory findings. Certainly the electrocardiographic findings need not be "characteristic," any more than they need be for the diagnosis of infarction under other circumstances. It is more important that, in association with other clinical evidence, they show *changing* patterns over a period of days

The difficulties of timing the onset of infarction plague the physician

Case 5. A 50 year old man complained of precordial pain while engaged in his duties of inspecting amusement park equipment The apparatus on which he was riding had stopped with an unexpected jar Evidence of infarction rapidly developed and he died early the following morning The patient had denied having any symptoms previously. Postmortem examination showed a posterior wall infarction which appeared to be *not less than 10 days old. Inquiry among his* associates revealed that he had had a 1 hour bout of "indigestion" and vomiting about 2 weeks before death

The infarction in this case was related to the earlier episode and not to that of the day before death. Without the autopsy findings, an erroneous conclusion would probably have been reached.

In my opinion Blumgart's criteria should be revised in the following way, recognizing that these are *minimal* criteria only; the physician *cannot, with clear conscience,* state that a given activity produced a given infarction unless· (*1*) cardiac symptoms develop during or soon after the alleged exertion, and (*2*) there is definite electrocardiographic evidence of recent myocardial damage

As the cases cited in this chapter show, in view of the variable course of the naturally occurring disease, it would seem that coronary occlusion and myocardial infarction resulting from trauma or effort are very uncommon but not unknown

The physician may be willing to state that an accident "might" or "could" have produced cardiac damage, the referee will seldom be satisfied by such testimony and may insist on a declaration that the doctor believes that it did produce such damage The doctor may then summon up all his knowledge and experience, satisfy his conscience if he can, stifle his misgivings, and answer the question, adding as much qualification as he is permitted In some instances, he may have to refuse to respond categorically to the question as worded Referees and legislators will have to recognize that the medical expert is not trying to evade the issue, it is simply impossible in some cases to be certain about what happened

The solution, so far as it is a solution, for the doctor is First, to give his opinion with honesty and dignity Second, and perhaps more important, to remember that he is a physician and not a lawyer or a lawmaker, the inequities of a given law or the abuses which may result from their interpretation may deeply concern him as a private citizen, but when testifying as a medical expert he must forego indignation and exasperation and allow the courts to interpret his testimony as they see fit

The solution for society would seem to be to remove such a highly controversial issue from the field of litigation Recent proposals to treat heart disease, no matter how caused, as an illness to be covered by industrial insurance, seem to provide a sensible solution.

INSURANCE BENEFITS AND CORONARY DISEASE

Coronary disease may enter into questions involving insurance benefits in three ways

1 It may be alleged that the claimant fraudulently concealed earlier history of heart disease In the absence of telltale physical signs at the time of the initial examination or of the subsequent disclosure of a history of coronary disease, it is practically impossible to hold that an insuree had had coronary disease before the insurance policy was issued unless a routine ECG was taken It is true that some ill individuals will run even this gauntlet, but most patients with degenerative heart disease will present some evidence of it in the ECG.

2. Under the terms of certain policies, the insuree may claim benefits to be paid in case of permanent and complete disability In the past, many life insurance policies contained provisions for the payment of benefits in the event of total and permanent disability. Most companies have discontinued such policies, thus sparing the cardiologist from making difficult, sometimes impossible decisions

The physician is called upon to decide whether the claimant has heart disease and, if so, whether it prevents his earning a livelihood A redefinition of terms has gradually evolved through judicial interpretation, and "permanent" and "total" disability no longer, in this connection, have their original, literal meanings It is not necessary for him to certify that the disease is beyond the possibility of eventual cure for it to be considered "permanent." Most policies carry the provision that if an illness lasts beyond a given time, it is to be considered permanent

"Total disability" no longer carries with it the implication that the patient cannot earn a living in any way A man with certain skill *and training, such as a physician, is not* expected to earn his living as night watchman or peanut vendor, although physically he might be able to do so The previous training and experience of the patient must be given serious consideration and if he is unable to carry on the same or comparable work without risk to himself, he is "disabled totally "

The recent change in our attitude toward the prognosis of coronary disease and our understanding of the psychologic principles involved, has diminished considerably the number of patients who consider themselves or who are considered by their physicians as incapable of earning a livelihood.

3. Some policies provide for the payment of double benefits in case of accidental death, and the question sometimes arises about the relationship of a given accident to death in the case of a person with heart disease When a man with known heart disease dies during an accident, it is important to know whether he was actually killed by the impact or whether the accident was the result of an immediately preceding fatal heart seizure In my experience, most such problems arise from claims for double indemnity for vehicular accidents. No rules can be formulated to assist the doctor or insurance companies in these matters; each case must be decided on the basis of the history, the clinical findings, and the results of autopsy. The following brief histories, taken from my own files, will illustrate these points.

Case 6 A 39 year old man had angina pectoris and electrocardiographic evidence of myocardial damage (bundle-branch block). He was driving alone on a dry country road when observers noted his car swerving, seemingly out of control, off the road, crashing into a tree and killing the driver Postmortem examination showed advanced coronary sclerosis, recent thrombosis of a main vessel, and infarction of the left ventricle, apparently several days old

In this case, of course, it would be impossible to attribute his death entirely or even largely to the accident

Case 7. A 62 year old man had known, but clinically mild, coronary disease Against medical advice, he took a long journey by automobile, New York to New Orleans, entirely alone He was found dead, crushed within a demolished car, at a concrete fence The road was dry and there were no skid marks Autopsy showed advanced arteriosclerosis of all the coronary arteries, old myocardial fibrosis, but no point of coronary occlusion or recent infarction Inquiry showed that he had driven over 400 miles that day and was trying to reach a motel a hundred miles farther on at which he had made reservations

There are several possibilities here He may have had a seizure of cardiac pain and driven off the road, he may have died suddenly, the car crashing thereafter, he may have fallen asleep at the wheel, he may have swerved to avoid hitting an animal. Since in this case obviously no definite answer could be given by the physician, the problem had to be resolved by negotiation or judicial decision; a compromise was reached to the satisfaction of claimants and the insurance company.

Case 8 A 45 year old man with a history of coronary disease was killed when his car hit a police stanchion. Autopsy showed numerous injuries and advanced coronary atheromatosis without recent occlusion or infarction It was an icy evening and investigation revealed definite skid marks.

Here again, one couldn't be sure, but the diagnosis of accidental death was not challenged

MEDICOLEGAL ASPECTS OF THE ELECTROCARDIOGRAM

I have repeatedly emphasized that the ECG is of definite, but only limited, value A diagnosis can be made with complete certainty from the tracing alone only in the case of certain arrhythmias, and even in these only the nature of the rhythm is established, not the nature of the underlying disease In coronary disease and myocardial infarction, the ECG is an aid in varying degree, depending on the type and location of the lesion. In some cases, especially of chronic coronary disease, the tracing is suggestive, sometimes highly so, but in all cases the tracing must be interpreted in the light of clinical findings.

It cannot be emphasized too strongly that the ECG reflects the anatomic changes in the heart, and is *not* a measure of the functional capacity of the heart. A tracing may show marked deviation from normal, and yet the individual may be able to lead an active life with vigorous exercise; on the other hand, the ECG may be normal in the presence of the most advanced heart failure.

Serious errors may be made in interpreting a tracing which is only slightly abnormal. The limits of variation in size and shape of the complex are normally wide, inexperienced physicians have often exaggerated the importance of minor changes in borderline records. Furthermore, the influence of extracardiac agents on the ECG must be borne in mind, the effects of changes in posture, the influence of drugs, respiration, neural stimuli, diseases in other organs, which may affect skin resistance, etc, or influence the heart only reflexly, must all be observed

If the following limitations on the use of the electrocardiograph, as laid down by Marvin,[12] are taken into account, courts and lawyers will be less likely to entertain extravagant claims of the value of the ECG

1. Changes in the ventricular complex, including its terminal portion, have no special significance, except the changes associated with myocardial infarction

2 The ECG hardly ever gives helpful information on the functional state of the heart; therapeutic questions about the amount of rest and action and the proper dosage of digitalis therefore cannot be decided on the basis of the ECG

3 It is usually impossible to give a prognosis from the ECG

4 The graphic records must be interpreted in the light of clinical evidence. Many physicians are making unjustified diagnoses of heart disease solely on strength of minor variations

TABLE 28 RELATIVE IMPORTANCE OF ELECTROCARDIOGRAM IN DIAGNOSIS OF HEART DISEASE[14]

Etiology	Pathology	Function
Congenital III	Developmental Defects III	Congestive Failure IV
Rheumatic III	Valvular Damage III	Cardiac Asthma IV
Syphilitic III	Arterial Damage III	Angina Pectoris IV
Arteriosclerotic II	Muscular Damage	Limitation of activity IV
Hypertensive II	A Degeneration or destruction of the myocardium II	Causes of increase of cardiac symptoms
Asthmatic II		
Thyrotoxic III	B Relative myocardial weakness (especially in a heart already damaged) IV	Increase in pathologic lesions IV
Pneumonic III		
Diphtheric III		Increase in work IV
		Abnormal rhythm I
Toxic II	Pericardial Damage II	Bacterial Endocarditis [illegible]
Traumatic II	Abnormal Rhythm I	

I Diagnosis may be made by the ECG alone

II Diagnosis usually, or frequently, is confirmed or corroborated by electrocard[illegible] evidence

III Diagnosis may be aided by the ECG under some circumstances

IV Diagnosis is not helped by the ECG

in the ECG; these should never be accepted in the absence of supporting clinical evidence

The original ECG, and not merely its interpretation, should be in evidence and available for reading by expert witnesses The qualifications of those who are to interpret the tracings must be well established Neither the possession of an electrocardiograph nor the ability to take attractive tracings confers skill in interpretation Certification by qualifying boards or qualifications equally exacting should be insisted upon.

It must also be borne in mind that a single tracing is of limited value Serial tracings, preferably taken as soon as possible after an injury alleged to have produced cardiac injury, with repeated follow-up tracings, give a much clearer picture of dynamic processes, especially when a particular incident is involved. Even better would be a control ECG, taken either as part of a program of routine health examinations or of the physical examination given to prospective employees, which would make it much easier to evaluate subsequent changes.

Table 28 indicates the amount of help which may be expected in various heart conditions, from the use of the electrocardiograph

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